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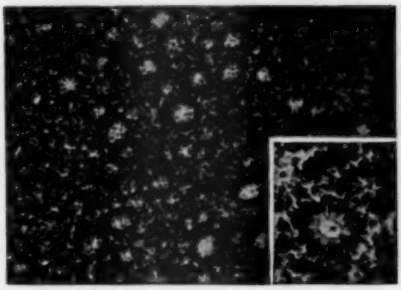

Figure 52; Page 76

By
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VOLUME 53 FEBRUARY 1952 NUMBER 2

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GRANULOMATOUS ENCEPHALOMYELITIS IN INFANCY

J. P. WYATT
ST. LOUIS
AND
W. W. TRIBBY
MEMPHIS

THE GENESIS, the morphologic aspects, and the fate of inflammatory lesions occurring in the central nervous system of infants have been clouded for years by Virchow's concept of congenital interstitial encephalitis.[1] Although, in rare instances, agents of a viral, fungal, or metallic nature [2] have been labeled as producing lethal encephalomyelitides, it is only within the last 10 years that infection, particularly that due to Toxoplasma,[3] has been recognized as a dominant agency in the production of infantile encephalomyelitis.

In this contribution six examples of fresh and healing granulomatous encephalomyelitis, of diverse causation and of variable duration, are reported. One of these six instances is the second case of encephalomyelitis due to the salivary gland virus to be reported. Another showed the morphological features of a distinctive type of encephalopathy only recently described by Sabin. The total of six cases of granulomatous encephalomyelitis, all possessing unusual features, is used to develop the discussion of encephalomyelitis in infancy. As the terminal results of these destructive inflammatory diseases on the brain have not been previously emphasized, this important phase of the problem is amplified.

REPORT OF CASES

CASE 1.—S. G., a 6-week-old white girl, was admitted to the hospital, poorly nourished, with a history of passing dark-colored urine, being feverish, feeding poorly from the bottle, and, twenty-four hours prior to admission, undergoing convulsions. The infant had been a premature delivery at eight months. No histological examination of the placenta was carried out at the obstetrical hospital. The mother and the father were in good health, and both had negative results from serum tests for syphilis. A first-born child, 1½ years old, was well developed and in good health.

Examination in the hospital revealed a lethargic infant, with irregular twitching of the hand, generalized spasticity, and exaggerated reflexes. The hospital course was characterized by a fluctuating temperature that at times reached 103.5 F. The circumference of the head was

From the Department of Pathology, St. Louis University (Dr. Wyatt), and Methodist Hospital, Memphis, Tenn. (Dr. Tribby).

1. Virchow, R. L.: Arch. path. Anat. **38**:129, 1867; **38**:472, 1868.

2. Neal, J. B.: Encephalitis: A Clinical Study, New York, Grune & Stratton, Inc., 1942.

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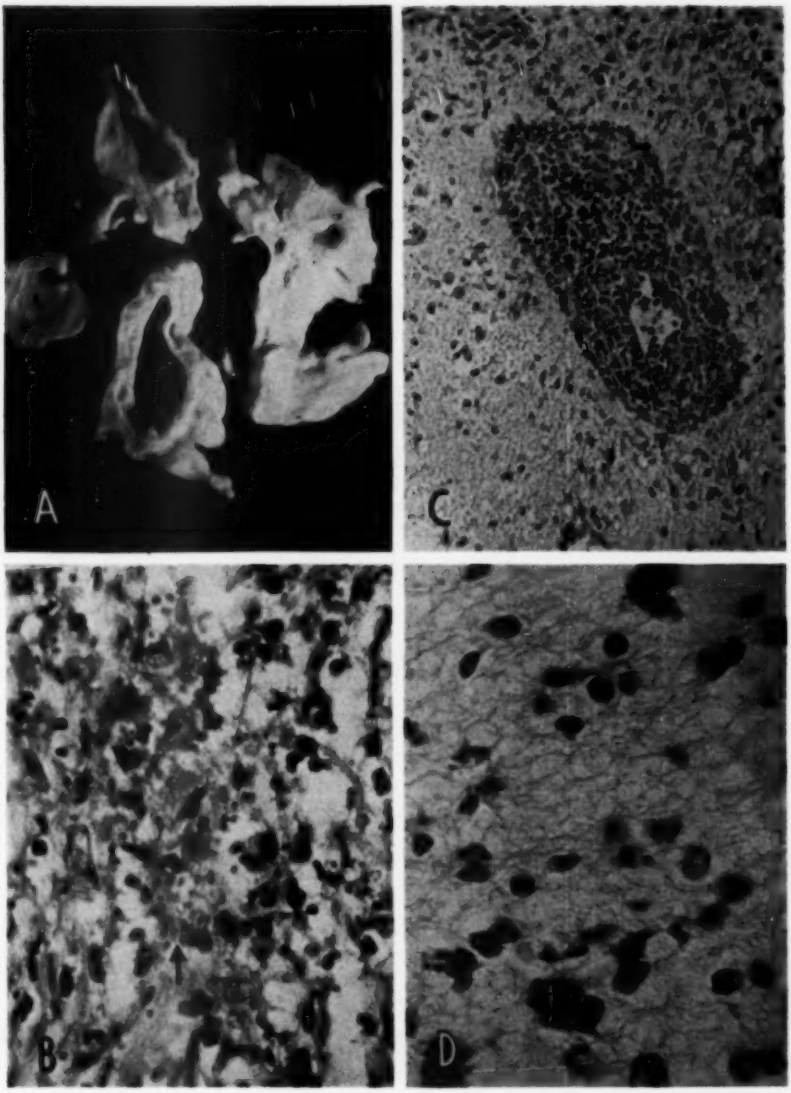

Fig. 1.—*A*, transections of the brain of an infant (Case 1) revealing extensive destruction, with a "moth-eaten" appearance in some regions and definite cyst formation in other areas. Hemorrhage (black) involving ganglionic nuclei may be noted, as well as dilatation of a ventricle.

B, numerous extracellular Toxoplasma organisms (arrow) associated with an inflammatory response and astrocytic proliferation in Case 1. Hematoxylin and eosin; × 360.

C, intense "periarteritis" in an inflammatory reaction surrounding a blood vessel in Case 2. The inflammatory response is composed of polymorphonuclears, eosinophilic granulocytes, and monocytes. Proliferation of astrocytes may be noted. Hematoxylin and eosin; × 320.

D, discrete deposits of calcium associated with astrocytic proliferation in Case 2. Hematoxylin and eosin; × 520.

39 cm., with marked separation of the sutures, and the anterior fontanel was bulging and tense. Roentgenological examination revealed an internal hydrocephalus with severe dilatation of the right ventricle. No punctate calcification was seen.

Laboratory Findings.—Moderate anemia was indicated by a red cell count of 3,930,000 per cubic millimeter and a hemoglobin reading of 10 gm. per 100 cc. The clotting time was 2 minutes. The white cell count was 18,000 per cubic millimeter, with 60% granulocytes present in the differential count. Ventricular puncture was performed, the cerebrospinal fluid giving cell and protein readings as follows: that from the left ventricle, 182 polymorphonuclears per cubic millimeter and 670 mg. of protein per 100 cc.; that from the right ventricle, 182 polymorphonuclears and 760 mg. of protein. Aerobic and anaerobic cultures of the spinal fluid were negative. Five days after admission the infant underwent a prolonged convulsion and died.

Gross Examination.—The infant showed loss of tissue turgor and bulging, tense fontanels and protuberant eyes. No other external markings were noted. The remarkable macroscopic findings were in the brain. There was extensive honeycombing of the periaqueductal, periventricular, extraganglionic, and subcortical regions. In these regions there were irregular cystic channels filled with opaque yellow fluid, communicating one with the other. In close apposition to this "moth-eaten brain" there was yellow, granular, crumbling brain tissue. Streaks of bright hemorrhage were noted throughout the necrotic brain substance, particularly around the ganglionic regions (Fig. 1*A*). A few of the cystic cavities were lined by a porcelaneous wall, simulating the wall of a porencephalic cavity. In some respects the gross findings mimicked those usually labeled encephaloclastic porencephaly.[4]

Histopathological Examination.—Within the brain, particularly in the upper pontine, juxtabasal-ganglionic, periventricular regions and in the centrum ovale, there was widespread encephalomalacia. The softened tissue was made up of fluid-filled cysts with a surrounding astrocytic basket work. The tissue destruction was profound, leaving mainly a vascular skeleton throughout the degenerated areas. In some regions dense astrovascular scars formed prominent scaffolds incarcerating the larger cystic pockets. Debris made up of necrotic neutrophilic and eosinophilic polymorphonuclear material was scattered throughout but was most heavily concentrated in the periventricular regions. Toxoplasma organisms were numerous, filling macrophages and scattered singly throughout the necrotic regions (Fig. 1*B*). These organisms were crescentic in shape and had definite nuclear formation. In many regions the toxoplasmic pseudocysts were in close apposition to the vascular templates.

The remainder of the organs were free of pathological changes. There was no dissemination of parasites in the other viscera, such as the myocardium, the liver, the spleen, the adrenals, or the kidneys.

In order that a more concise report may be rendered, the pathological diagnosis of the six cases reported in this contribution will be recapitulated following the histopathological discussion of Case 6.

Case 2.—C. M., a month-old white girl, a feeding problem from birth, was admitted to the hospital because of feverishness and convulsions. This infant was two weeks premature, delivered by induced labor. On admission a temperature of 102.6 F., bulging, tense fontanels, generalized twitching, spasticity of the upper limbs, unequal pupils, and ptosis of the right lid were noted. The infant was severely dehydrated.

Laboratory Findings.—On the day of admission the red blood cell count was 2,780,000 and the hemoglobin content was 11 gm.; the white cell count was 9,830, with metamyelocytes 12%, band cells 10%, segmented cells 58%, monocytes 2%, and lymphocytes 18%. Three days later the red cell count was 2,680,000 and the hemoglobin content was 9.5 gm.; the white cell count was 2,920, with 16% band cells, 44% segmented cells, 4% monocytes, and 18% lymphocytes. Urinalysis gave negative results on several samples. The blood calcium was 8.8 mg. per 100 cc. The spinal fluid was xanthochromic and under considerable pressure, with a total protein content of 285 mg.; it showed 7 leucocytes and 2 red blood cells per cubic millimeter; the result of the colloidal gold test was 0 in all 10 dilutions; there was a chloride reading of 700 mg. The Kahn test was negative on blood and spinal fluid. Cultures for organisms under aerobic and anerobic conditions were negative. Roentgenological examination of the chest revealed clear

4. Baar, H. S.: Brit. M. Bull. **4**:178, 1946.

lung fields. The infant continued to have generalized convulsions, nystagmoid movements, and Cheyne-Stokes respiration. Throughout the five days in the hospital the course was stormy, with a fluctuating temperature. Despite administration of succinylsulfathiazole, subcutaneous fluids, and oxygen, the infant died in a convulsive seizure.

Gross Examination.—At autopsy this month-old girl weighed 2,900 gm.; the skin was wrinkled, and there was considerable loss of tissue turgor. No rash was noted. The fontanels were tense but not bulging. There was no protuberance of the eyes.

The outstanding gross lesion was encountered in the brain. The lateral ventricles were moderately dilated. The fluid within the ventricles was opaque and of a shimmering yellow appearance. The aquaeductus cerebri was completely closed, and the periaqueductal tissue was swollen and yellow white, and cut with a firm, gritty sensation. Cut section revealed the lesion to be well delimited, and on cursory examination it was a replica of a pontine glioma. Within both posterior portions of the third ventricle and the roof of the fourth ventricle there were a few foci of roughened ependymal lining. The remainder of the viscera were not remarkable.

Histopathological Examination.—The outstanding feature was the widely disseminated characteristic granulomatous lesions of toxoplasmic encephalitis. In the larger lesions there was central necrosis, resembling superficially the caseation of tuberculosis. Toxoplasma organisms were scanty in these necrotic lesions but were present within bordering cells and occasionally lying free. There were banal inflammatory cells beneath the ependyma. As the reaction to Toxoplasma has been emphasized previously in the literature,[5] only pertinent comments will be inserted in this description. Cavitation and granulomatous response, conventional hallmarks of toxoplasmic infections, were well delineated in this case. Lying in the honeycombed brain were small groups of Toxoplasma organisms. Encystment of the parasites was frequent; in particular, the host parasite cysts nestled close to the vascular templates. The vessels showed intense angiitis, with an occasional eosinophile in the perivascular infiltrate (Fig. 1*C*). The glial knots and granulomas were miliary and submiliary in type. Calcification was well demonstrated by Von Kossa's stain, the granules being delicate, punctate, and diffuse, especially beneath the ependymal lining (Fig. 1*D*).

In the lungs there was an interstitial inflammatory reaction, with many large mononuclears and a few neutrophiles in the alveolar walls and alveolar spaces. There were a few mononuclear cells in the stroma of the pancreas and rare focal areas of fibrosis.

All the remaining viscera except the myocardium were free of Toxoplasma and inflammatory changes. The myocardium, almost free of inflammatory changes, showed a few scattered intrafascicular Toxoplasma cysts, indicative of contented symbiosis.

Case 3.—R. P., a 5-week-old white boy with a birth weight of 3,400 gm. had failed to gain in weight after a premature delivery. This infant had been short of breath since birth, with intermittent bouts of cyanosis. The family history was noncontributory, with two siblings alive and well. The temperature on admission was 98 F., and there was no temperature recording above 100 F.

Laboratory Examination.—The red cell count was 4,850,000, with a hemoglobin content of 14.8 gm. The white cell count was 10,300, with a differential count showing neutrophiles 55%, band cells 2%, monocytes 4%, eosinophiles 3%, and lymphocytes 36%. Kolmer's test was negative on both blood and spinal fluid. The spinal fluid was sterile, xanthochromic, with chlorides and sugar not remarkable, and the total protein was 249 mg. After a severe convulsion the pulse dropped to 20 beats per minute and the infant suddenly died, five days after admission to the hospital.

Gross Examination.—The body was that of a well-developed, fairly well-nourished white boy 5 weeks of age. The body measured 51 cm. in length and weighed 3,020 gm.

The brain was soft, with the convolutions and sulci regular in pattern. The white and the gray matter of cerebrum and cord were intact. Multiple sectioning revealed a small organizing blood clot in the choroid plexus in the left lateral ventricle. The remaining viscera were not remarkable.

Histopathological Examination.—The lungs showed areas of collapsed alveoli, and other portions of the lung contained edema fluid and hemosiderin-laden macrophages. The bronchioles

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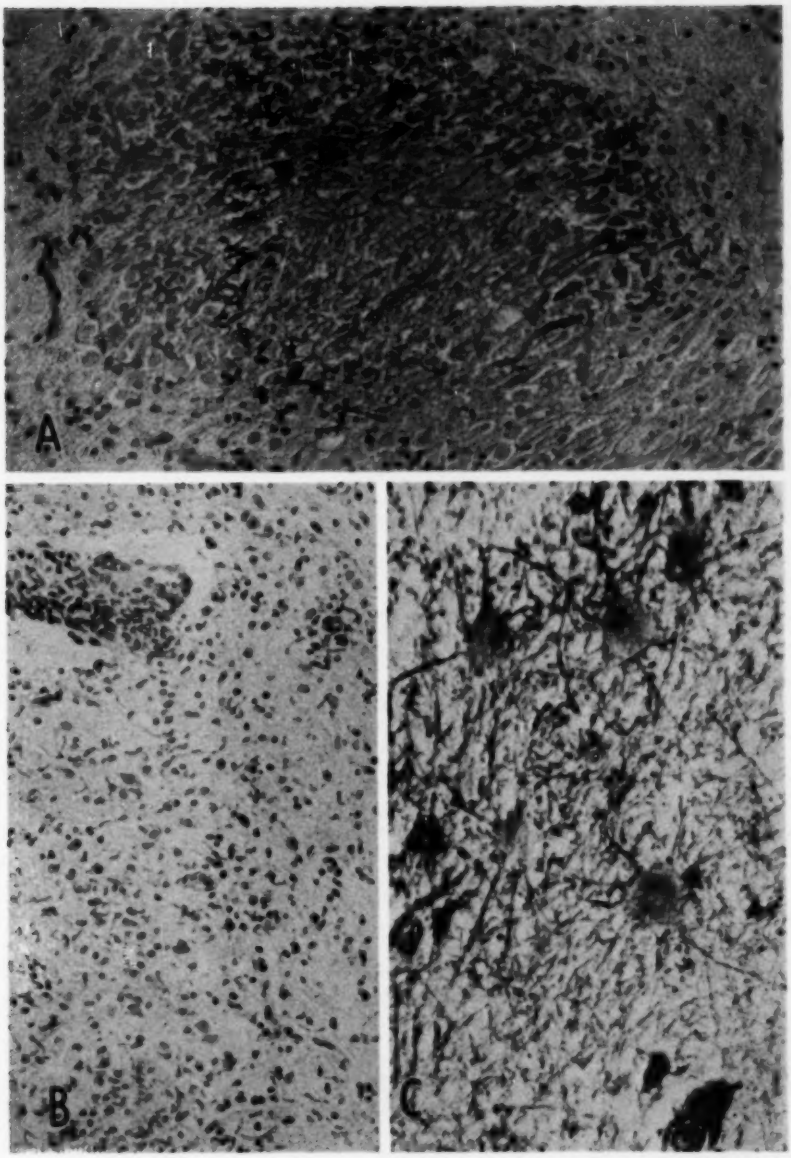

Fig. 2.—*A*, well-defined granuloma with a necrotic center and a peripheral court composed of bloated astrocytes, polymorphonuclears, and calcium-encrusted glial fibers in Case 3. Hematoxylin and eosin; × 400.

B, markedly increased cellular content made up of poorly defined granulomas, rod-cell multiplication, and intense perivascular inflammatory reaction (case 4). Hematoxylin and eosin × 220.

C, noteworthy proliferation of astrocytic and microglial elements in Case 4. Phosphotungstic acid-hematoxylin; × 360.

were free of pathological changes. There were occasional neutrophilic cellular casts in the lumens of the collecting tubules of the kidneys; the parenchymal, interstitial, and vascular tissues of the kidneys were normal. Other organs (heart, liver, adrenal, pancreas, spleen, thymus, lymph nodes, marrow) were free of any inflammatory or degenerative alterations.

Within the brain, particularly in the walls of the lateral ventricles and the subependymal regions of the hypothalamus and periaqueductal regions, there were numerous circumscribed granulomatous lesions. The central areas of these necrotic granulomas (Fig. 2*A*) were composed of an amorphous eosinophilic granular material. The periphery was made up of reticular, astrocytic elements and elongated fibrils which stained blue-black, highly characteristic of linear streaks of calcific material. Rod-shaped microglia cells were seen surrounding foci composed of dark granules of calcium. Scattered throughout the white matter were a few to moderate numbers of heterogeneous inflammatory cells. An occasional vessel showed perivascular cuffing with lymphocytes. In the subependymal plate some polymorphonuclear and mononuclear cells were present. All vessels were congested. Granulomas were undergoing karyolytic changes, with rupture and spillage of the nuclear debris over the demarcating granuloma borders. In the left lateral ventricle there was a small well-organized thrombus which was intimately related to the choroid plexus and presented a tangled skein of fibroblastic tissue, lime salt deposits, and vascular buds. Enmeshed in this disrupted network of choroid plexus were hemosiderin-laden macrophages. Acid-fast stains were negative. No Toxoplasma or any other etiologic organisms could be demonstrated in the necrogranulomatous lesions. Despite the failure to demonstrate Toxoplasma, on the bases of the histopathologic observations, it is contended that in this particular instance the encephalitis is best explained as due to toxoplasmic infection.

Case 4.—F. B., a white boy, with a normal delivery and with a birth weight of 3,800 gm., suddenly, at the age of 16 days, was unable to feed from the bottle because of protracted vomiting. On the day of admission he became deeply cyanotic immediately after a feeding.

The temperature on admission was 97 F.; the respirations were of the gasping type. With oxygen, the cyanosis cleared, but extreme lethargy persisted. The only movement elicited was in the left arm and leg; the patellar, Achilles, biceps, and abdominal reflexes were absent.

Laboratory Findings.—The red cell count was 5,300,000; the hemoglobin content, 16 gm. The leucocyte count was 11,400, with band cells 5%, segmented cells 65%, lymphocytes 27%, and monocytes 3%. The spinal fluid was xanthochromic and sterile on culture for aerobic and anaerobic organisms; the total protein content was 140 mg. and the chloride content 780 mg. The result of the colloidal gold test was 0 in all 10 dilutions, and the cell count was 188 polymorphonuclears per cubic millimeter. The Kolmer test was negative on both blood and spinal fluid. This infant was treated with continuous oxygen, subcutaneous fluids, penicillin, and aureomycin. Lethargy and cyanosis persisted despite therapy, and during an episode of Cheyne-Stokes breathing the infant suddenly died.

Gross Examination.—The body was that of a 16-day-old white male infant, relatively well developed and nourished. The upper part of the trunk and the face were cyanotic. No scars or evidence of recent or remote trauma to the head was noted. The lungs were heavy and doughy, with patchy congestion of the lower lobes. The cut surface was firm and dry. No adhesions or enlargements of the bronchial lymph nodes were noted. Heart, lungs, spleen, pancreas, gastrointestinal tract, kidneys, adrenals, and brain were free of pathological alterations.

Histopathological Examination.—In the lungs there was stuffing of the alveoli with squames of amniotic origin; this aspirated foreign material was remarkably well preserved. Both a giant cell and a foam cell reaction were associated with the aspirated material; the foam cells were most prominent in the peripheral zones of the lung. The bronchi were free of these cells. Although the neutrocytic reaction was light, there were a prominent mononuclear reaction and intense capillary congestion.

In the liver the hepatic cord cells were intact, pale staining, with granular degeneration of the cytoplasm. In the spleen the venous sinuses were filled with red blood cells and intravascular aggregates of mixed hematopoietic elements. Hemosiderin pigment was also present. The remainder of the pulp was not abnormal. In the kidneys hydropic and granular degeneration was present in the convoluted tubules; the remainder of the renal structure was unaltered. Congestion was prominent in other viscera.

The cerebral cortex and the cerebellum revealed no evidence of hemorrhage. The cortical laminations were normal in appearance, but stratification and cellular content were disturbed,

owing to a few aggregations of microglia cells found within the precentral cerebral cortex. In the pons, the medulla, and the hypothalamic regions there was a focal granulomatous reaction with necrosis around the ependyma and the perivascular spaces (Fig. 2*B*). The typical granuloma consisted of astrocytes and microglial rods as satellites around neurons showing degeneration. Proliferation of the astrocytes and tremendous rod cells was noteworthy (Fig. 2*C*). The granulomas spread out into the surrounding parenchyma. These inflammatory foci with their mixed cellular make-up were intimately associated with the perforating vessels. The vascular channels showed perivascular cuffing with lymphocytes and plasma cells. The elongated rod cells were again prominent in the outer courts of the mesodermal lesion. Beyond the reaches of the inflammatory foci the neurons, astrocytes, and other supporting glia were intact. This inflammatory response was particularly well demonstrated in the gray matter of the medulla and the hypothalamus.

Case 5.—R. R., a 13-week-old white boy, was first admitted to the hospital five days after birth with diffuse purpura of the skin and enlargement of liver and spleen. The mother had had no previous pregnancies. Both mother and baby were Group A, Rh positive. There was no accumulation of Rh antibodies in the mother's serum. No familial history of blood diseases was obtained. Serological tests for syphilis in infant, mother, and father were negative. Hematological studies on first hospital admission revealed a red cell count of 2,400,000 with a few erythroblasts in the smear, and a platelet count as low as 80,000 per cubic centimeter. Urinalysis repeatedly gave negative results. A clinical diagnosis of congenital thrombocytopenic purpura was made. Infusions of concentrated compatible red blood cells were given. The infant was discharged with improvement in clinical signs but with persistence of hepatosplenomegaly. On the second admission, three weeks later, there were an elevated temperature, frequent bloody stools, vomiting of fresh blood, and a blood nonprotein nitrogen content of 54 mg. per 100 cc. The enlarged spleen and liver were more noticeable. The white blood cell count slowly increased from 11,000 to 30,000 per cubic millimeter, with an absolute increment in metamyelocytes and myelocytes. Fifty-three erythronormoblasts per 100 white blood cells were noted in the smear. The platelet count remained around 40,000 per cubic millimeter, with a normal bleeding and clotting time. Frequent bloody stools intensified the dehydration. Despite repeated transfusions of compatible bank blood, the anemia remained severe, with counts as low as 2,100,000 red blood cells. Aspirated bone marrow revealed a normal differential count for an infant of this age. Labored respirations, cyanosis, and disseminated purpura were pronounced immediately prior to death. The clinical diagnosis was thrombocytopenic purpura and diarrhea, cause undetermined.

Gross Examination.—The autopsy was performed on a markedly dehydrated, poorly nourished 13-week-old white male infant. The fontanels and the eyeballs were collapsed. The liver weighed 55 gm. and was firm in consistency, with discrete red-gray patches on a dark brown background. The spleen weighed 20 gm. and was firm and dark red. The terminal ileum contained several mucosal erosions, averaging about 2 mm. in diameter. The kidneys were not enlarged. Their cortices were pallid, smooth, and sharply demarcated from the brownish red medulla. No other noteworthy macroscopic observations were made.

Histopathological Examination.—Within the liver, lung, kidney, pancreas, small intestine, and brain were the characteristic inclusions of the salivary gland virus. As the emphasis in this contribution is on the cerebral lesions, only a résumé of pertinent histological information needs to be given on the other involved viscera.

The liver structure was preserved, with an occasional focus of granulocytic and normoblastic cells within the sinusoids. The inclusion-laden cells were sparse in number and almost exclusively situated in the bile duct channels. Within the lungs there was an irregular mononuclear septal pneumonitis. An occasional characteristic large cell with nuclear and cytoplasmic inclusions was noted. No bacteria were demonstrated with a Gram stain. In the kidney a large proportion of the proximal convoluted tubules showed widespread involvement of the epithelium. The cells were gigantic in outline, and in places the lumens were occluded completely by the nests and clusters of the singularly large cells burdened with inclusions. Surrounding many of these altered tubules were infiltrating mononuclears. The glomeruli and the vascular elements were negative.

The brain showed early dilatation of the lateral ventricles and of the Sylvian aqueduct. Widely disseminated throughout the subependymal regions, particularly beneath the lateral ventricles, there was a striking inflammatory reaction. This inflammatory response was also encountered in the subcortex, the upper pontine region, and the thalamic nuclei. Lymphocytes and

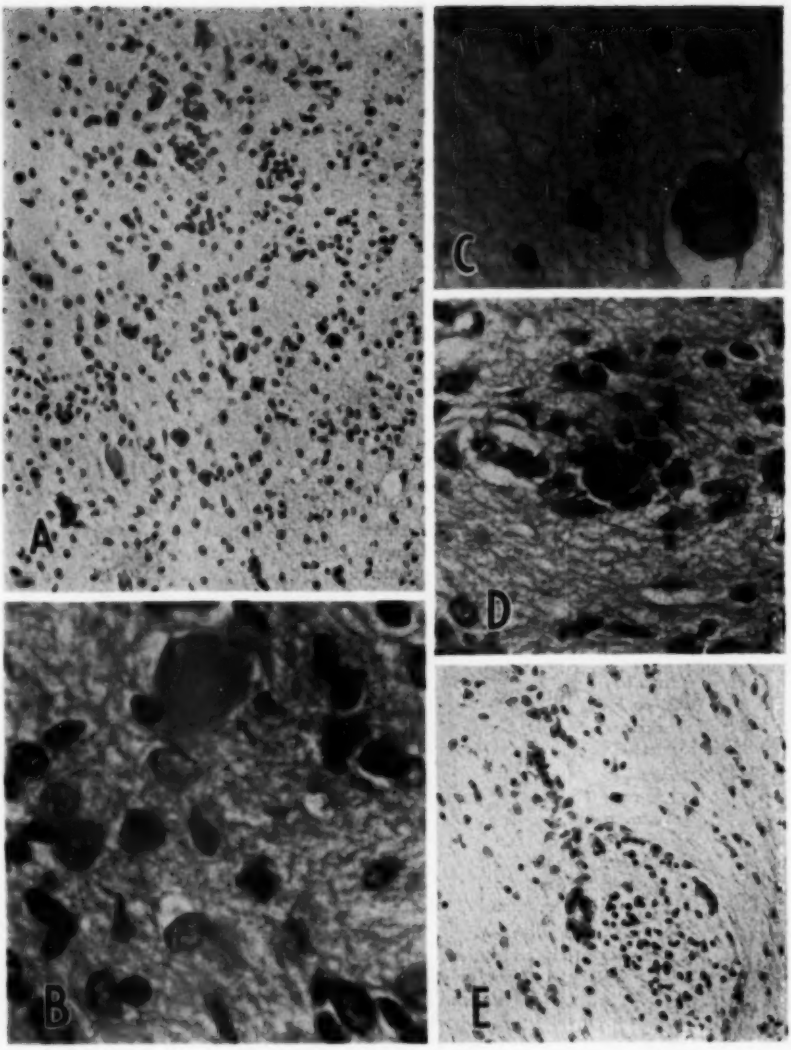

Fig. 3.—*A*, increased cellular content of white matter, lymphocytic foci, and discrete calcification. Hematoxylin and eosin; × 120.

B, inclusion-laden cell surrounded by numerous astrocytic elements. The intranuclear inclusion, the wrinkled nuclear membrane, and the bloated cytoplasm are characteristic of salivary gland virus. Hematoxylin and eosin; × 600.

C, "owl's eye" intranuclear inclusion (arrow), swollen cytoplasm, and granular cytoplasmic inclusions at periphery of inclusion-burdened cell. A perivascular lymphocytic infiltrate is present. Hematoxylin and eosin; × 600.

D, salivary gland virus inclusion in a disintegrating phase. Hematoxylin and eosin; × 600.

E, granulomas of mononuclear cells associated with delayed maturation of subependymal cell matrix. Hematoxylin and eosin; × 100.

plasma cells predominated and were arranged into miliary groups and knots (Fig. 3*A*). Frequently in the center of these inflammatory foci were bloated astrocytic or microglial elements. These cellular components, particularly astrocytes, contained both intranuclear and intracytoplasmic inclusional structures characteristic of the salivary gland virus (fig. 3*B*, *C*, and *D*). These inclusional structures were in the florid stages as well as in phases of decadence. In the center of the inflammatory alterations calcification was intense. The lime salts in the form of incrustation of decadent nerve elements was noteworthy. Another cardinal alteration was the spotty calcification noted in the outer mesodermal layers of the vessels throughout the affected regions. Ependymal granulations and disruptions of the subependymal matrix were outstanding changes in this brain (Fig. 3*E*). The myocardium, the spleen, the lymph node, and the thymus were free of pathological alterations.

Case 6.—F. W., a white female infant was admitted to the hospital at the age of 9 weeks because of lethargy, sporadic vomiting and twitching of the face. Six weeks prior to hospital admission, both parents had noticed an "increasing tenseness of the skull." Delivery of the infant had been normal, with labor lasting four hours. Both parents and siblings of the infant were healthy.

On physical examination, June 23, 1947, the infant weighed 4,500 gm., and the skin was remarkably dry. There was evident separation of the cranial sutures, with the fontanels large and tense, and the head measured 38 cm. in circumference. The deep reflexes were exaggerated, and the temperature was 99.2 F.

Laboratory Findings.—On June 23 there were 4,510,000 red blood cells per cubic millimeter, with the hemoglobin content 12.5 gm., and 14,750 white cells, 48% of which were segmented cells, 43% lymphocytes, 7% monocytes, and 2% eosinophiles. Serum cholesterol was 119 mg. and calcium 9.7 mg. per 100 cc.; the Kahn and Kline tests of the blood were negative. The cerebrospinal fluid protein was 200 mg., sugar 63 mg., and chlorides 680 mg. per 100 cc. Bacteriological cultures and animal inoculations gave negative results.

Follow-up studies of the cerebrospinal fluid gave the following results. Aug. 12: 5 lymphocytes, 250 mg. of protein, and no bacterial growth; Aug. 22: 8 lymphocytes, 1,125 mg. of protein, and no bacterial growth. On Aug. 12 smears of spinal fluid showed no Toxoplasma. Antibody tests for Toxoplasma (rabbit method) were negative on blood from both mother and patient.

Roentgenological Studies.—On June 24, anteroposterior and lateral views of the skull (Fig. 4*A*) revealed extensive calcific deposits throughout the meninges of the calvaria and of the base of the brain. These deposits were granular and were laid down in flat plaques of a circular, linear, or ovoid shape. There was no tendency for the calcification to extend into the falx. The bones of the skull were conspicuously underdeveloped. Long bones of the upper and lower extremities and of the trunk were normal. Chest, lungs, and heart were normal.

Later roentgenological examinations may be summarized as follows. Aug. 28: Anteroposterior and lateral views of the skull revealed a definite increase in the size of the cranial vault but no apparent alteration in the calcific deposits. Sept. 5: The ventriculogram showed both ventricles tremendously dilated, filling the bony cranium. No cerebral cortex was demonstrable. The roentgenological diagnosis was hydrocephalus with blockage at the level of the foramen of Monro. Nov. 13: The ventriculogram showed abnormalities similar to those found previously. The thickness of the bones of the skull was definitely greater than normal and described as "surprising for hydrocephalus of such long duration" (Fig. 4*B*).

Course in Hospital.—The temperature averaged around 99 F., but varied between 98 and 104.6 F., being sustained between 100 and 103 F. for one week in October. The terminal temperature was 103.6 F. The child gained weight very slowly, reaching a maximum of 6,400 gm. on Nov. 9. Thereafter the weight decreased, reaching 4,500 gm. on Feb. 4, 1948. The circumference of the head increased, reaching 50 cm. on Oct. 17, 1947; on Feb. 2, 1948, it measured 47 cm. A generalized maculopapular rash of undetermined cause appeared on Oct. 5, 1947; this rash persisted for approximately one month. Spasticity of the neck and extremities was noticed sporadically throughout the stay in the hospital. On Dec. 29, 1947, a biopsy specimen of the left parietal region of the brain was obtained. The histopathological description of this is given below. The infant led a vegetative existence during the last three months of life. On Feb. 4, 1948, she became cyanotic, with shallow respirations, weak pulse, rigidity, and died on Feb. 5. Autopsy was performed five hours after death.

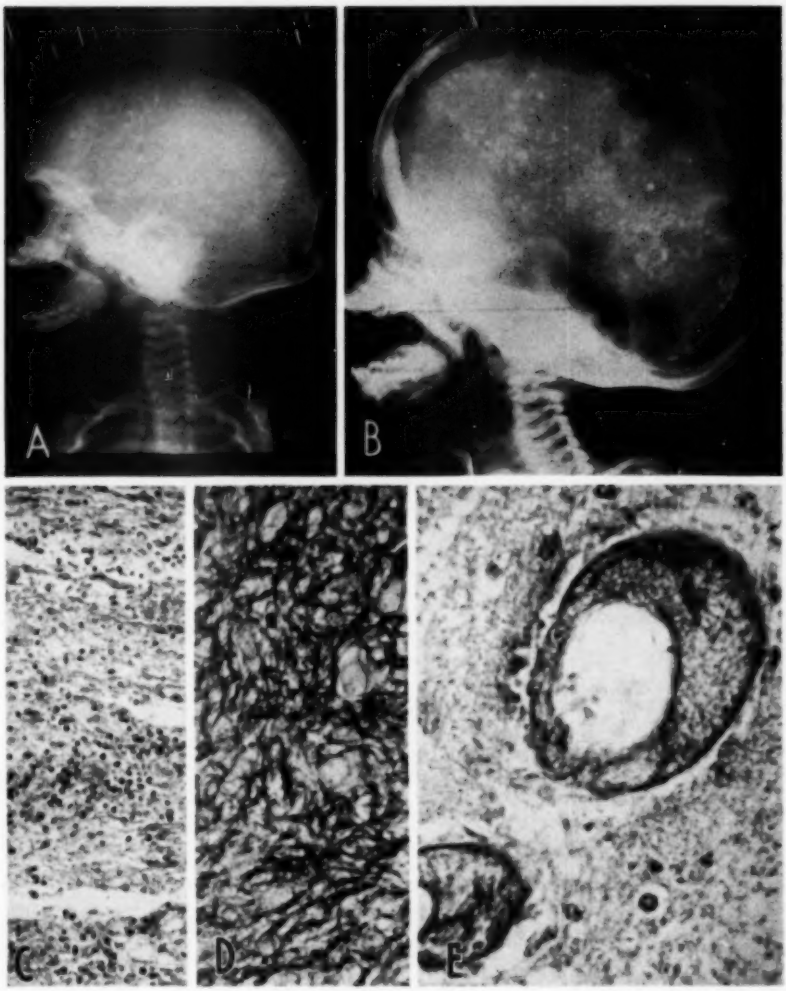

Fig. 4 (Case 6).—*A*, roentgenogram of skull eight months before death, infant aged 9 weeks. Note extensive calcification of the cerebrum.

B, roentgenogram of skull two and a half months before death. It reveals progressive calcification of the brain and enlargement of the head. *A* and *B* have the same photographic reduction to illustrate the increase in the size of the head.

C, extreme atrophy and disorganization of the cortex and the white matter due to diffuse granulomatous vascular alterations. Hematoxylin and eosin; × 180.

D, dense gliosis producing a felt work of glia fibers. Phosphotungstic acid-hematoxylin; × 180.

E, eccentric fibrinoid vessel change and spotty calcification encroaching on blood vessel lumens. Phosphotungstic acid-iron hematoxylin; × 400.

Gross Examination.—The body was emaciated, weighing 4,400 gm. and measuring 57 cm. in length. The skin was dry and wrinkled. The head measured 17 cm. in anteroposterior diameter and 11 cm. transversely. The anterior fontanel measured 8.5 by 4.4 cm. There was a healed left occipitoparietal scar in the scalp, 8 cm. long. A healing osteoplastic bone flap, beneath the scar, measured 8.0 by 3.2 cm. There were two membranous, thin regions in the skull, on the right and left sides in the parietal portions, measuring 2.8 by 1.5 cm. and 4.4 by 1.5 cm., respectively. Exclusive of a severe loss of weight of most of the organs, abnormal findings of interest were confined chiefly to the head. After removal of about 900 cc. of clear, pale yellow intraventricular fluid, the brain weighed 260 gm. (normal, 750 gm.). The entire thickness of the cerebral tissue of the hemispheres varied from 0.3 to 0.5 cm. The septum pellucidum and the interventricular communications were not identified with certainty, since the interior of the brain consisted of a single, large, smooth-surfaced cavity. There were numerous adhesions between the dura and the pia-arachnoid. Many irregular, plaque-like, pale yellow calcific deposits were found in the cerebral substance, varying up to 0.5 cm. in diameter, most abundant around the base of the brain but not involving the medulla or the cerebellum. There was no dilatation below the level of the foramina of Monro, and these structures could not be found. The pituitary gland appeared normal. The eyes were removed, and were free of gross pathological changes. The other viscera were not remarkable.

Histopathological Examination.—The cerebral cortex showed atrophy of such a degree that the entire thickness of the tissue in some sections could be included in one low-power field of the microscope (Fig. 4*C*). Numerous foci of calcification were seen in the cortical tissue. There was dense gliosis adjacent to the calcific deposits (Fig. 4*D*), and in many regions fibrillary astrocytes were prominently displayed. Some venous channels had perivascular lymphocytic infiltration. The pia-arachnoid was considerably thickened and composed of highly vascular granulation tissue which contained scattered monocytic cells showing a tendency toward perivascular concentration. A striking feature was the presence of peculiar eccentric degenerative changes in some of the small blood vessels (Fig. 4*E*). These changes were manifest as acidophilic fibrinoid and sometimes granular material which thickened the vascular walls and apparently narrowed their lumens. Ganglion cells were sparse, degenerated, and difficult to identify. The choroid plexus was considered normal. A thorough search of many sections of the brain and eye failed to reveal any evidence of Toxoplasma or other organisms. In the eye there were foci of fibrosis on the inner surface of the retina, containing pigmented cells presumably derived from the choroid. The above histopathological description of alterations is based on the observations derived from the biopsy specimen of Dec. 29, 1947, as well as on those from postmortem sections of the brain.

RECAPITULATION OF PATHOLOGICAL DIAGNOSES

In case 1: widespread intracerebral toxoplasmosis; early hydrocephalus and porencephaly with focal calcification, and patent foramen ovale.

In case 2: focalized periaqueductal toxoplasmosis; obstructive hydrocephalus; interstitial pneumonitis.

In case 3: granulomatous encephalitis; early hydrocephalus; disruption of the choroid plexus with hemorrhage; edema and congestion of the lungs, and focal atelectasis.

In case 4: granulomatous encephalomyelitis, particularly pronounced in the pons, the medulla, and the hypothalamic regions; profound microgliosis; pneumonitis due to aspiration of amniotic material; patent foramen ovale.

In case 5: disseminated inclusion disease (salivary gland virus); granulomatous encephalomyelitis; early hydrocephalus with periventricular calcification; septal pneumonitis; ulcerative enteritis.

In case 6: "non-toxoplasmic vascular encephalopathy" (Sabin); interventricular glial nodules; pronounced hydrocephalus.

GENERAL COMMENT ON THE SIX CASES

Cases 1 and 2 were illustrative of the destructive effect exerted by Toxoplasma on the nervous system; only the locale of the disease process varied. In Case 1 the destructive encephalomalacic process was due to a heavy infection with easily demonstrable Toxoplasma organisms. In this instance the inflammatory process was diffuse, with extensive destruction of upper pontine, centrum-ovale and subcortical regions. Some of the cystic regions were lined by glial tissue akin to that associated with porencephalic cavities. This distinctive periventricular reaction was stressed by Frenkel,[6] who regarded this reactive sclerosing zone as somewhat analogous to the tissue reaction of hypersensitivity. These cystic cavities reached almost to the cortical surface and connected one with another. The early attempt at porencephalic formation associated with a replacement "internal hydrocephalus" was a prominent feature in this example. In contradistinction to Case 1, in Case 2 the occlusive granulomatous and calcific reaction was restricted almost exclusively to the periaqueductal region, simulating in the gross a pontine new growth.

In Cases 3 and 4 the focal nature of the lesions and the heterogeneity of the cytological response were pattern components which attested to the inflammatory nature of the process. It was considered that tuberculosis could be eliminated through inability to demonstrate the tubercle bacillus, complete absence of histopathological criteria for such a diagnosis, and the fact that the lungs and the choroid plexuses[7] were free from tuberculosis. Syphilis was excluded because of the negative Kahn test, and the morphological cadre present in the central nervous system was unlike that demanded for conventional hereditary syphilis.[8]

In Case 3 the frank granulomatous lesion was sharply demarcated, with the center of the structural alteration being partially necrotic. Surrounding this core of eosinophilic debris was a hematoxylinophilic barrier of calcium deposit associated with a palisade of distorted astrocytes. The basic change was a focal necrotizing granulomatous alteration, probably due to the action of Toxoplasma.

In Case 4, that of a 16-day-old infant, the perivenule arrangement of the inflammatory foci, the sharing of the mesodermal elements of the vessels in this reaction, and the location of the inflammatory lesion within the gray matter were pathological features supporting a viral genesis. Particularly, as Spielmeyer [8] emphasized some years ago, the absence of lipoid histiocytes in an inflammatory focus favored a diagnosis of primary encephalomyelitis. Further acceptable evidence supporting a viral origin consisted of intrinsic changes within the neurons, Nissl body dissolution, acute cytoplasmic swelling, and even complete dropping-out of the ganglion cells. The profound rod-glial response was encountered only in this instance and spread beyond the confines of the glial-lymphocytic knots. Although the neurons at some distance from the inflammatory foci retained their integrity, and no neuronal or glial inclusion bodies were encountered, there remained strong morphological evidence for a viral pathogenesis in this instance. The involvement of the precentral gyrus with inflammatory and dissolutive neuronal changes suggests the action of the poliomyelitic virus.

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In Case 5 the inclusion disease process was widespread but the greatest concentration of the reaction was in the regions of the lateral ventricles, with calcification an important alteration in the inflammatory reaction. Although Muller [9] in 1922 reported an example of salivary gland virus inclusion disease in which hydrocephalus was found, no mention was made of inclusional encephalomyelitis. Kinney [10] reported these unique inclusions within the brain although the encephalomyelitic reaction was not emphasized. Worth and Howard [11] have described recently a case of lethal fulminant encephalitis in which they claimed the salivary gland virus was the etiological agent. In Case 5 the dominating symptoms were reflections of hepatic, splenic, and marrow disturbances presenting the clinical picture of purpura, anemia, and leukemoid peripheral blood; these hematological findings overshadowed the manifestations of encephalitis. This masking of central nervous system lesions by more obvious signs and symptoms from other diseased organs may occur more frequently than usually credited.[12]

In Case 6 the extensive calcification, choroidal tract alterations, the unusual blood vessel changes, and the disseminated focal glial scars were all suggestive of toxoplasmic inflammation. But the evidence supplied by Sabin and Feldman [13] that the serological tests gave no indication of toxoplasmic infection shows that some agent other than Toxoplasma can initiate destructive lesions of the central nervous system producing a nonspecific picture of hydrocephalus and cortical atrophy manifested clinically as mental retardation and blindness.

With this description of a third distinctive central nervous system disorder by Sabin in 1949, three conditions in infancy may present as encephalitis, with subsequent hydrocephalus, intracranial calcification, and mental retardation: toxoplasmic infection, salivary gland virus encephalitis, and "Sabin's encephalopathy." These conditions can be differentiated on laboratory evidence.

Postvaccinal encephalomyelitis and allied diseases can be erased from the etiological analysis because of the onset, the nature, and the course of the illnesses. Lead and other metallic substances can likewise be eliminated as etiological agents in that the inclusion bodies within the viscera can be demonstrated and the metallic forms of encephalopathy are distinctive from that associated with viral inclusions. Again, in plumbism the cytological response is scanty and certainly not granulomatous.[14] Fungous infections, particularly torulosis, are frequently accompanied with diffuse destructive meningoencephalitis. The pathological aspect of fungous infections is usually distinctive, being of a widespread destructive nature, with the specific organism frequently visible in sections, showing capsulation, sporulation, or budding formations, with corroborative support from the serological or cultural evidence.[15]

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CONTRIBUTIONS FROM THE LITERATURE CONCERNING THE PATHOGENESIS OF INFANTILE ENCEPHALOMYELITIS

Historical Background.—Although Brissaud [16] in 1899 was the first to classify "encéphalopathes infantiles," every attempt at clarification of congenital or early infantile encephalomyelitis has been shadowed by Virchow's dicta on congenital interstitial encephalitis.[1] Particularly in the German literature, polemics [17] have been waged over the basic nature and causative mechanism responsible for perivascular crescents of "small round cells" and "gitter" elements. Scheyer [18] and Guillery [19] believed that these histological findings were the residues of normal development, whereas other authors have contended that Virchow's congenital encephalitis was the result of parturitional trauma [20] or a pronounced assault on fetal tissues due to maternal sepsis.[21] Globus [22] has pointed out that the cellular residues of the periventricular matrix in the subependymal zone and "perivascular infiltrates" which give the erroneous impression of inflammation are in reality undifferentiated neuroectodermal or microglial fountains of del Rio Hortega,[23] normally encountered in the developing brain of infancy. This basic confusion has in the past led to overt cases of encephalomyelitis being wrongly denominated as Virchow's encephalitis, whereas the reaction was probably a true inflammatory response evoked by some infectious agent.[24]

Evidence in Favor of Transplacental Transmission of Infection.—In the light of the recent observations of Gregg [25] and Swan [26] that cardiac anomalies, cataracts, deaf-mutism, and microgyria can be attributed in certain cases to maternal rubella occurring in the first trimester and that a maternal infection with the virus of Western equine encephalomyelitis leaves permanent mental changes in the newborn,[27] it is apparent that some revision of our ideas respecting the causation of these baffling perfidies of nature is needed.

An encephalomyelitis discovered in the first few days of life suggests an intrauterine infection transmitted from mother to fetus via placental pathways or break-

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through. It has been known for years that placental permeability exists and apparently increases with aging of the afterbirth; this feature has been stressed by several investigators.[28] Until 1939 Treponema pallidum was the only organism, easily demonstrated, which was known to violate the placental barrier, ultimately producing fetal death or sequential crippling distortions of the nervous system in the later infantile periods. Confirmation of the belief that the placental barrier is passed has been given recently by other pathological processes. From morbid-anatomical studies on infants stillborn from the effects of the salivary gland virus [29] and the finding of hemoprotozoa in endometrial curettings,[30] in spontaneous abortions, it is now generally accepted that certain infectious maladies have a transplacental mode of transmission.

Experimental Evidence in Favor of Intrauterine Brain Destruction by Infectious Processes.—In the field of experimental pathology Kostoff [31] has shown that viruses can cause quantitative deviations in the developmental processes and that a cell in which a virus has established residence has had a transmissible characteristic added to it not unlike a new gene.[32] Hamburger and Habel [33] with influenza virus A and Dawson [34] with the rabies virus have produced a high incidence of developmental deformities, particularly in the neuraxis of the maturing chick embryo. Experimental Toxoplasma infection of the early chick embryo [35] has resulted in profound alterations, such as destructive visceral malformations and extensive calcification, findings akin to those encountered in mammalian infections. These investigations indicate that embryonic brain offers a preferential medium for virus growth. The fact that Toxoplasma [36] and the salivary gland virus favor embryonic or fetal tissues, particularly brain, as a residence tissue may be readily explained by Goodpasture's suggestion [37] that the ready involvement of embryonic tissues may be due to the intrinsic active metabolism of such tissues or to the low level or absence of immunity processes.

With the initiation of destruction, further injury may follow, owing to flaring of the infection or some other biological phenomenon. Greenfield [38] has suggested that transsynaptic degeneration occurs with far greater rapidity, extent, and degree in the immature nervous system than in the mature. Hans Spemann [39] and others [40]

28. Windle, W. F.: Physiology of the Fetus: Origin and Extent of Function in Prenatal Life, Philadelphia, W. B. Saunders Company, 1940. Huggett, A. St. G.: Brit. M. Bull. **4**:196, 1946-1947.

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37. Goodpasture, E. W.: Science **95**:391, 1942.

38. Greenfield, J. G.: J. Neurol. & Psychiat. **1**:306, 1938.

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have shown that in the developing fetus chaotic and abnormal maturation, particularly of the nervous system, will result if dead foreign tissue is introduced into "developing centres." In the experimental animal perpetuation of destructive encephalomyelitis has been accomplished with the utilization of degradation products from liberated myelin.[41]

Ultimate Sequelae Following in Utero Brain Destruction.—Years ago, Schultze,[42] Strumpell,[43] and later, in 1921, Globus [44] emphasized the fact that congenital porencephalies might be due to infectious encephalitis of intrauterine origin. Laying particular emphasis on the late destructive effects of inflammation borne by the central nervous system, Dorothy Russell,[12] through recent morphological observations on infants, has advanced knowledge still further in this field. In some instances she demonstrated that hydrocephalus and possibly related deformities could be attributed to an inflammatory condition produced by living agents that seldom become established in the brain or the meninges of the adult. In furtherance of this premise, there is increasing evidence that permanent cerebral damage may develop after an episode of meningitis or encephalitis, perhaps undiagnosed originally, followed by a latent period of variable duration, which finally in some cases leaves grotesque results, such as hydrocephalus, multiple cystic conditions, or allied malformations.

Coexistent with or subsequent to inflammatory reactions of the brain, the reparative response may be profound or at times exaggerated. This repair phenomenon may be conditioned by or in conflict with intrinsic factors of development, although in the last few months of pregnancy most fetal organs have passed the critical period in which their morphogenesis can be directed into atypical channels. Not so with the developing brain, for in vertebrates the definitive morphogenesis follows through for a period of time after the newborn has been removed from intrauterine environmental influences. This continuing development may account for the remarkable and intense gliosis that is associated with certain smoldering viral encephalitides in the young.[45] Collateral evidence from other "inclusion encephalitides" would indicate that these disorders may have exceedingly protracted courses and initiate totally unexpected alterations which cripple and kill. These inflammatory processes may even produce lesions in the first decade of life, usually associated with senile involution.[45] Owing to the basic properties of nerve tissue, residual lesions are conspicuous. The finale of the disease processes depends not only on the intensity of the infection and the degree of involvement but also on the ability and the briskness with which nerve cells regenerate. Inability of nerve cells to regenerate after anatomic violation contributes to more extensive and permanent damage. Hence the pathologic alterations of hydrocephalus, porencephaly, and possibly other deformations may be partially explained on an outright destructive basis as well as on that of mechanical interference with cerebrospinal fluid flow.[46]

41. Rivers, T. M.; Sprunt, D. H., and Berry, G. P.: J. Exper. Med. **58**:39, 1933.
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From all of this it should be realized that frequently developmental arrest is only the indicator of the time of damage [47] and not the expression of a faulty tendency of the tissue. With the intrauterine inception of disease, whether due to Toxoplasma,[30] the salivary gland virus, or some other cryptic agent, it is quite possible that progressive and permanent damage will develop *in utero*. Subsequently, with death in the infantile period, it may be difficult to recognize the inflammatory nature of the *in utero* insult. On superficial examination the brain deformity will appear to be an innate perversion, but on closer scrutiny the true status of the defect may be recognized.

Other Factors Involved in Intrauterine Brain Destruction.—It is not denied that in many instances hydrocephalus [48] and microgyria, alone or in conjunction with regimented anomalies, such as locomotor deformities, cutaneous dystrophies, and vascular defects, may be of a provenance entirely different from that of the "infectious mutilative" types under discussion. In some instances disseminated encephalomalacia with multiple cavity formation may be attributed to trauma as Schwartz [49] has stressed, or may even, conceivably, represent forms of diffuse cystic sclerosis of Schilder's type.[50] Evidence derived from the field of comparative pathology indicates that demyelinating cavitation disease develops in newborn lambs following a copper deficiency in pregnant ewes.[51] Furthermore, it has been shown that nutritional impairment is capable of producing hydrocephalus; when folic acid antagonists were added to the maternal rat diet there was a great increase in the incidence of hydrocephalus in newborn rats.[52]

Although it is recognized that the evidence presented in support of the probability that infection plays a prominent role in the evolution of "destructive anomalies" of the infantile brain is not conclusive, the support of such a doctrine, emphasized by the investigations of Wolf, Cowen, and Paige,[38] is all-important for future studies in this field.[4] Thus fetal abnormalities [28] may have a duality of causation, both genetic inclination and environmental provocation being influenced by intrauterine infections.

From the aftermaths of disease it may be difficult, through morphology alone, to label the inciting agent; as Savage [53] said years ago, "the debris in a wrecked house is the same whether the fire originated in lightning or a paraffin lamp." Other methods, such as cultural or serologic analysis, are of the utmost importance in the investigation of these "infectious brain deformities in infants." Far too often these disorders of the central nervous system receive a hasty burial in a museum pot.

47. Meyer, A., and Cook, L. C.: J. Ment. Sc. **85**:258, 1937.

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SUMMARY AND CONCLUSION

Six cases of granulomatous encephalomyelitis in infants are reported. Two cases were of demonstrable toxoplasmic causation, and in one instance the intracranial lesions were caused by the salivary gland virus. In the remaining three cases the morphological evidence strongly suggests an infectious origin. In the six cases the duration of illness varied from 16 days to 8 months. The clinical manifestations were protean, and in several of the examples the ultimate sequels were hydrocephalus, porencephalic healing, extensive gliosis, and change of vascular pattern.

This study supports the view that some examples of brain deformities previously believed to be of genetic origin may in reality represent the end-results of infectious mutilation.

The serological studies and the history of Case 6 are published with the permission of Dr. A. B. Sabin, Cincinnati, and Dr. G. Levy, Memphis, Tenn.

DISSECTING ANEURYSM OF THE AORTA

Pathologic Aspects
An Analysis of Eighty-Five Fatal Cases

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VIRTUALLY all of the present concepts regarding dissecting aneurysms have been based on analyses of small groups of cases or even of single cases. Such a meticulous and inclusive review as Shennan's [1] incorporated only 28 cases which he had himself observed over a period of many years. Although the major pathologic details have been presented precisely and repeatedly,[2] debatable points are often only reiterated rather than settled by a poll of authors. Accurate appraisal of the pathologic descriptions, clarification of apparent contradictions or discrepancies, and the placing of proper emphasis on seemingly minor details require uniform study of a large group of cases. To the end that the entire problem may be viewed in proper perspective, the significant episodes in the development of knowledge of dissecting aortic aneurysms will be briefly reviewed.

The first unmistakable pathologic description of a dissecting aneurysm is generally attributed to Morgagni.[2a] Nicholls, in 1761, described an unruptured, "incipient" aneurysm in George II of England, who died of a ruptured right ventricle.[1] Though the cases of Maunoir,[3] 1802, and of Shekelton,[4] 1822, could readily be identified from the reports, the term "dissecting aneurysm" and the recognition of the lesion as an entity date from the second edition of Laennec's [5] treatise on

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1. Shennan, T.: Dissecting Aneurysms, Medical Research Council, Special Report Series, No. 193, London, His Majesty's Stationery Office, 1934.

2. (*a*) Sailer, S.: Dissecting Aneurysm of the Aorta, Arch. Path. **33**:704-730 (May) 1942. (*b*) Shennan.[1]

3. Maunoir, J. P.: Mémoires physiologiques et pratiques sur l'anevrisme et al ligature des artères, Geneve, J. J. Paschaud, 1802.

4. Shekelton, J.: Dissections of Aneurism, Dublin Hosp. Rep. **3**:231-240, 1822.

5. Laennec, R. T. H.: Traité de l'auscultation médiate et des maladies des poumons et du coeur, ed. 2, Paris, J. S. Chaudé, Libraire-Éditeur, 1826; cited by Shennan.[1]

auscultation, 1826. Shekelton is to be credited with the first description of the chronic form of the disease; in each of his two cases of "aneurysmal tumors," blood circulating through the new sac within the wall of the aorta reentered the original channel at a lower point.

Subsequently pathologic details were unfolded at an accelerated rate. The experience of 120 years merely serves to substantiate the description of Elliotson.[6] Writing in 1829, he noted that the internal rupture is usually transverse, that the external tear is frequently longitudinal, and that both occur most often in the ascending aorta. Furthermore, he considered disease of the wall of the aorta of primary importance, recognizing that even on the most strenuous exertion normal vessels are not subject to rupture. Pennock,[7] 1838, and Henderson,[8] 1843, independently noted that dissection occurred within the media, the latter even localizing it to the outer portion of that layer. In 1863 Peacock,[9] who had previously observed and reported 5 cases, was able to compile a total of 80 from the literature; these included 8 of long standing. Numerous authors, beginning with Rokitansky[10] in 1839, described the microscopic details and discussed the pathogenesis of the process.

Clinical diagnosis of dissecting aneurysm dates from the case of Swaine and Latham,[11] 1856. Though Shennan found only 6 acceptable instances of the clinically diagnosed disease, 33 had been reported by 1939,[12] and by 1944 the figures had risen to 59.[13] An increase in clinical enlightenment and acuity is reflected by Bauersfeld's[14] report in which the antemortem diagnosis was correct in 6 of 15 cases.

The reported incidence of dissecting aneurysm at autopsy averages about 1 in 381 cases.[15] Sailer found 24 among 11,131 autopsies (1 in 464) over a period of 20 years. Three thousand, one hundred twenty-nine autopsies at the University of Maryland included 12 in which dissecting aneurysms were observed; these constituted 25% of all aortic aneurysms.[13]

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6. Elliotson, J.: On the Recent Improvements in the Art of Distinguishing Diseases of the Heart; Being the Lumleyan Lectures Delivered Before the Royal College of Physicians in the Year 1829, London, Longman, Rees, Orme, Brown & Green, 1830.

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13. Leitch, W. H.: Dissecting Aneurysm, with Case Report, Bull. School Med. Univ. Maryland **29**:7039, 1944.

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15. Holland, L. F., and Bayley, R. H.: Dissecting Aneurysm: A Report of 19 Cases with a Review of the Recent American Literature, Am. Heart J. **20**:223-235, 1940.

The age group 40 to 60 years exhibits the greatest incidence, though the age of patients in reported cases ranges from 3 months [16] to 100 years.[1] Males are twice as often affected as females even though beyond the age of 60 the number of females becomes proportionately greater.[1]

MATERIAL AND METHODS

The clinical records and autopsy protocols of 85 fatal cases of dissecting aortic aneurysm furnished the data which are considered in this text. Slides and tissues permitting microscopic examination of the diseased aorta were available in 72 cases. In each instance, multiple sections of the aorta were examined, prepared with the following stains: hematoxylin and eosin, Masson's trichrome, Weigert's elastic tissue stain counterstained with Van Gieson, and Mayer's mucicarmine. In addition, selected slides representative of all lesions observed were stained for reticulum by the Wilder technique, for calcium by the method of von Kóssa, for mucin and reticulum by the periodic acid Schiff reaction. Similarly, in chosen instances, frozen sections were prepared and stained for fat with oil red O.

TABLE 1.—*Age Distribution in Eighty-Five Cases of Dissecting Aneurysm of Aorta*

Age Groups	Cases	
	Number	Per Cent
Under 20 yr.	1	1
20-29 yr.	18	21
30-39 yr.	13	15
40-49 yr.	14	17
50-59 yr.	20	24
60-69 yr.	13	15
70-79 yr.	4	5
80-89 yr.	2	2
Total with age known	85	100

CLINICAL FEATURES

The Army source of a considerable amount of this material (32 cases) weighted the distribution in favor of the younger age groups, as comparison of Table 1 with other reports quickly demonstrates.[2] However, proper allowance for the relative youthfulness of those included from the military population discloses the predilection of the disease for the older individual. There were only 6 (7%) women in this group. Nine (11%) of the patients were Negroes, a percentage in proportion to that of Negroes in the general population. Leitch [13] had found men to be affected twice as frequently as women, and white persons four times as frequently as Negroes.

PATHOLOGIC OBSERVATIONS IN EIGHTY-FIVE CASES OF DISSECTING ANEURYSM

Grossly the aortas which were the seat of dissecting aneurysm often showed a considerable but variable increase in external caliber. This was determined largely by the size, position, and extent of the intramural hemorrhage. The deformity produced could be described as saccular or fusiform; frequently, internal bulging produced significant luminal narrowing. In seven cases, all nonsyphilitic, the vessel exhibited a true aneurysmal dilatation of the vascular channel in addition to the intramural dissection. Six of the seven aneurysms were fusiform, involving the

16. Holle, G.: Über mehrfache angeborene mesenchymale Defektbildungen mit "Medionecrosis aortae" bei einem 3 monate alten Säugling, Ztschr. ges. Inn. Med. **2**:502-510, 1947.

ascending and the proximal segment of the aorta. Five of the seven were associated with congenitally bicuspid aortic valves; the two others, with a minor degree of isthmic stenosis.

Cardiovascular syphilis, substantiated clinically, occurred in only one case; but since the syphilitic lesions were separate from the dissecting aneurysm, the case is properly included in this series. Finally, there was a small saccular aneurysm of the abdominal aorta attributed to severe arteriosclerosis in a patient 86 years of age; it was clearly not related to a dissecting aneurysm of the arch.

Hypertrophy of the heart was present in 47 (73%) of the 64 cases in which information concerning this feature was available. Table 2A lists the differences between the maximum allowable "normal" figures [17] and the recorded heart weights. In 13 of the 47 cases (Table 2B) hypertrophy could be explained as an effect of valvular deformity and dysfunction. In the absence of a mechanical basis for

TABLE 2.—*Cardiac Hypertrophy in Cases of Dissecting Aneurysm of Aorta*

A. Excess of Heart Weight Over Normal

	Cases	
	Number	Per Cent
No excess (less than 74 gm. above maximum normal)	17	26
Probable excess (heart weight in excess of 400 gm. but body weight unknown)	5	8
75-149 gm. above maximum normal	16	25
150-224 gm. above maximum normal	3	5
225-299 gm. above maximum normal	11	17
300 or more gm. above maximum normal	12	19
Total with data	64	100

B. Cardiac Hypertrophy in Relation to Hypertension

Total with hypertrophy	47	73
Hypertrophy secondary to valvular heart disease	13	20
Hypertrophy presumably hypertensive	34	53
Clinical hypertension without hypertrophy	3	..
Total with hypertension	37	58

enlargement, hypertension was considered the most probable cause in 34 cases with hypertrophy limited principally to the left ventricle. In most of them, disseminated arteriolar changes or lesions known to be associated with increased arterial pressure were present. Furthermore, a good correlation existed between these anatomical features and a clinical diagnosis of increased blood pressure.

The aortic intima was smooth and without atheromatous or arteriosclerotic change in 18% of the cases. In an additional 15% such lesions were considered only mild. Frequently the prosector noted loss of elasticity, unusual friability of the aortic wall, and in several instances, including all of those with true luminal aneurysms which had preceded dissection (predissection aneurysm), reduction of its thickness. In the older group, as is to be expected, intimal disease was much more frequent. Appreciable arteriosclerosis was present in all except three individuals more than 31 years of age. The deformity and linear wrinkling of the intima overlying an area of medial degeneration were occasionally indistinguishable from

17. Smith, H. L.: The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age, Am. Heart J. **4**:79-93, 1928.

those caused by syphilis. The presence of intimal plaques and reactive (to hemorrhage) adventitial thickening added further to this resemblance (Fig. 1*A*). Occasionally there was a grossly obvious medial defect which permitted cleavage or splitting of the aortic wall on mere manipulation.

Site of Intimal Tear.—The intimal tear through which arterial blood entered the wall of the aorta was found in the proximal segment of that vessel in most

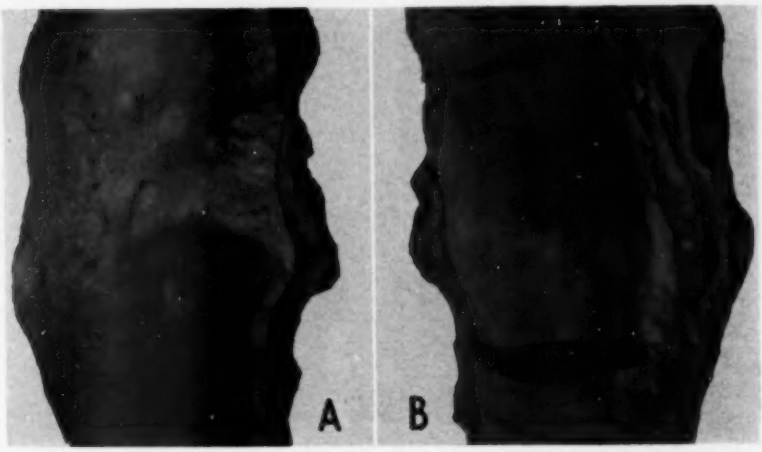

Fig. 1.—*A*, dissecting aneurysm of the thoracic aorta of four to five months' duration in a white man 52 years of age. Observe the plaques and the linear wrinkling of the intima. The intimal tear is angulate and predominantly transverse, with rounded edges. Armed Forces Institute of Pathology (AFIP), Accession No. 36557, Negative 50415.

B, external aspect of the aorta depicted in *A*. The dark roughened area at the summit of the aneurysm is the site of the external rupture which caused death. AFIP Acc. 36557, Neg. 50414.

TABLE 3.—*Anatomic Site of Initial Intimal Tear in Eighty-Five Cases of Dissecting Aneurysm of Aorta*

Location	Cases	
	Number	Per Cent
Ascending aorta	53	63
Transverse aortic arch	15	18
Distal aortic arch	8	10
Thoracic aorta	6	7
Abdominal aorta (including renal artery in one case)	2	2
Total	84 *	100

* Two anatomically distinct tears were present in each of five cases (AFIP Accessions 201601, 109502, 147440, 170292, 208946). In six others (AFIP Accessions 95745, 110990, 116973, 204134, 129581, 256625) there was no interruption of intimal continuity.

instances. There was no tear in 6 cases. The actual sites listed in Table 3 correspond with those previously reported in the literature.[2]

It was often observed that the tear was directed transversely to the long axis of the vessel (Fig. 1*A*). In the 55 specimens adequately described, the orientation was transverse in 21, longitudinal in 12, angulate in 8, and oblique, oval, or irregular in 6, 5, and 3, respectively. All five of the oval tears were found in chronic

dissecting aneurysms, and their margins were rounded and well endothelized (Fig. 1*A*). Since the time of Elliotson many authors have commented on the frequency of transverse tears in cases of dissecting aneurysm,[18] and it is probable that the circular orientation of the residual undamaged fibers supplies the explanation for this phenomenon. In this series the direction of the tear varied strikingly with the age of the patient. Whereas the tears were transverse or longitudinal in 50% and 14%, respectively, of individuals over 40 years of age (53 cases), comparable figures were 24% and 34% in those under 40 years of age (32 cases). The orientation was closely related to the histologic type of medial disease present and was not,

TABLE 4.—*Location and Extent of Intramural Dissection in Cases of Dissecting Aneurysm of Aorta*

Location and Extension	Cases	
	Number	Per Cent
Ascending aorta		
alone	10	12
and transverse aorta	16	19
and distal arch of aorta	4	5
and thoracic aorta	4	5
and abdominal aorta	30	35
Transverse aorta, distal arch, thoracic and abdominal aorta	8	9
Distal aortic arch		
and thoracic aorta	2	2
and abdominal aorta	4	5
Thoracic aorta		
alone	1	1
and abdominal aorta	4	5
Abdominal aorta	2	2
Total	85	100

TABLE 5.—*Location of Hemorrhage in Eighty-Five Cases of Dissecting Aneurysm of Aorta*

Location	Cases
Pericardium	32
Mediastinum	14
Pleural cavity, left	9
Pleural cavity, bilateral	5
Pleural cavity, right	4
Retroperitoneal	2
Total cases with external rupture *	69

* External hemorrhage was absent in 16 cases.

as Holland and Bayley [15] have implied, related to the segment of the aorta involved. Tears involving aortas with predominantly elastic medial disease (limited in this series entirely to individuals younger than 40) were 50% longitudinal, and there were no transversely oriented intimal lacerations. The finding probably reflects the loss of the usual circular alinement of the medial musculature associated with destruction of the elastic laminae. The lacerations varied considerably in length, ranging from 0.5 to 18 cm.; in two instances, the entire circumference of the vessel was involved. The location and the extent of the dissecting aneurysms are listed in Table 4.

18. Weiss, S.: Clinical Course of Spontaneous Dissecting Aneurysm of Aorta, M. Clin. North America **18**:1117-1141, 1935.

Arteriosclerosis, frequent and often severe in the older age groups, seemed to have no consistent relation to the site of the intimal laceration, since in only two instances did the laceration coincide with a sclerotic plaque.

Dissection often extended for a considerable distance within the walls of the aorta and into its branches. There were 19 cases in which the vessels to the lower

Fig. 2.—Chronic rechanneled dissecting aneurysm. The patient, a 40-year-old Negro man with known hypertension and angina, had been having congestive heart failure for four months when he died of cerebral hemorrhage. Observe the hypertrophied left ventricle, the oval (dark) defect in the proximal aorta, and the irregular gaping linear reentry tear distally. The margins of both defects are rounded. AFIP Acc. 47063, Neg. 63773.

extremities were involved. The basic process was identical whether the dissection tracts were long or short, and we therefore agree with Sailer [28] in considering together so-called "spontaneous" perforation or rupture and long dissection of the more classic type.

Secondary Rupture.—Despite the frequency of dissections extending into the abdominal aorta and its bifurcation (see Table 4), all but two external ruptures occurred within the thorax (Fig. 1*B*). The location and the number of these hemorrhages are listed in Table 5.

Mediastinal hemorrhage alone occurred only twice; it was present in seven instances of hemopericardium and in every case in which bleeding into the pleura was a feature. Considering the anatomic relations and the delicacy of the tissues involved, the tendency for hemorrhage to break out of the mediastinum is readily understood. Hemopericardium, on the other hand, was frequently isolated.

Among the 19 cases with unspecified sites of external rupture, the location of the fatal hemorrhage suggested that the sources were essentially the same as in the cases in which this information was provided.

The dissecting hemorrhage failed to break from the confines of the aortic wall in 16 instances. In four of these, internal rupture and rechanneling of the dissection tract had permitted relatively prolonged survival (Fig. 2). Such an event, however, provided no assurance that an external break would not occur subsequently: there were seven additional cases with a rechanneled dissecting aneurysm in which a fatal hemorrhage occurred from a week to two years after the onset of symptoms indicative of the initial lesion. Usually the terminal hemorrhage resulted from a new dissecting aneurysm entirely separate from the older tract (e. g., Armed Forces Institute of Pathology [AFIP] Accession 170292). In one noteworthy case (AFIP Acc. 95745) an intramural hemorrhage extending for 12 cm. in the thoracic aorta was associated with neither external nor internal lacerations. The absence of an intimal break, as seen in six instances (Table 3), did not preclude the possibility of an external tear since the terminal event in two of these cases was hemopericardium.

HISTOPATHOLOGIC OBSERVATIONS BASED ON SEVENTY-TWO CASES OF DISSECTING ANEURYSM OF THE AORTA

In each of the aortas examined microscopically a focal degenerative process was observed at multiple sites in the media. Such lesions were usually most severe in the region of the primary intimal tear in the arch of the aorta but were by no means limited to that area. They were also found widely scattered throughout the length of the aorta and even in some of its branches.

Depending on whether the muscle or the elastic laminae were primarily involved, two varieties of degeneration were observed. In a large group of cases the two types coexisted, but even among these, focal areas indicated their essential independence. For purposes of making the distinction between lesions of these types it was often necessary to examine multiple sections, because secondary factors frequently came into play when the media had been split by hemorrhage. Ischemic necrosis of smooth muscle was commonly noted in areas where the vascular supply had been obviously impaired or disrupted by the hemorrhagic dissection. Although such changes undoubtedly contributed to the extension of an already initiated dissection, they are and should be readily distinguished from the basic initial lesion. Variable accumulations of chromatrophic or mucinous material were frequently noted, especially in degenerative lesions of the elastica, where they sometimes formed fluid-filled cystic spaces. This substance was not observed in the absence of a structural

lesion, though medial degenerative changes unaccompanied by mucin accumulations were noted.

Medial Degeneration Limited to Muscle.—Normally the muscle fibers of the aortic media insert into the elastic laminae and serve in an auxiliary fashion to prevent overstretching and to facilitate recoil of this tissue. Degeneration of muscle is, therefore, conspicuously signaled by changes in the arrangement of the elastic laminae. In our sections there was loss of the normally wavy pattern and the fibers appeared stretched and attenuated. Furthermore, depletion of the muscle separating the elastic fibers permitted them to fall together. The process was focal, and in

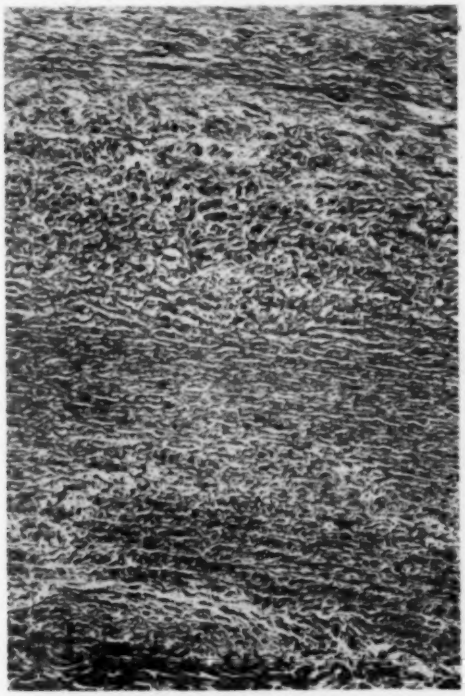

Fig. 3.—Depletion of muscle fibers in the middle third of the aortic media. AFIP Acc. 116312, Neg. 104314. Hematoxylin and eosin stain; × 90.

stained sections absence of muscle cells and nuclei could be readily recognized, even at low magnification, by the relative pallor of such areas (Fig. 3). Stains for elastic tissue demonstrated condensation of the laminae.

Disintegration products of the muscle cells were not ordinarily demonstrable; it seems likely, therefore, that the process does not exceed the speed of humoral absorption. Occasionally residual fibers in an area of degeneration were found to be swollen and vacuolated, presumably a manifestation of metabolic disturbance. The vacuoles, which were large and irregular, were nonlipid in nature (Fig. 4). However stains for fat revealed moderate numbers of minute extracellular droplets

Fig. 4.—Striking vacuolation of the muscle fibers in the aortic media. AFIP Acc. 112351, Neg. 104312.

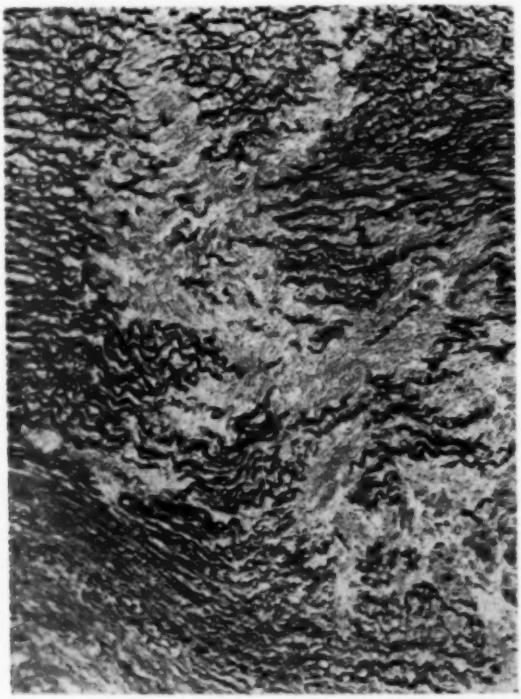

Fig. 5.—Focal disruption and loss of elastic laminae in the aortic media. AFIP Acc. 179691, Neg. 104291. Weigert's elastic tissue stain; × 55.

Fig. 6.—Only fragmentary remnants of the elastic laminae persist. There is an accumulation of "mucoid material" which divides the unaffected muscle fibers into geographic areas. AFIP Acc. 160866. Weigert's elastic tissue stain; × 62.

Fig. 7.—With loss of the elastic fibers in the inner half of the aortic media there are disarray and retraction of the persistent muscle cells. AFIP Acc. 107254, Neg. 104307. Hematoxylin and eosin stain; × 55.

scattered between the elastic laminae. In an occasional instance, tiny granular deposits of calcium were to be found similarly disposed, and it seemed reasonable to regard them as a consequence of the presence of extracellular fatty products of cellular disintegration.

Occasionally, small quantities of loose, poorly cellular fibrous tissue (myxomatous), containing mucin or chromatrophic substance, appeared between the elastic fibers to replace the depleted muscle, but cystic accumulations were not observed.

Medial Degeneration of the Elastic Tissue Type.—Focal loss of the elastica as seen in this series may involve only short segments of a few laminae or all of the laminae in a segment of the aorta extending through several low-power microscopic fields (Figs. 5 and 6). It was frequently associated with the accumulation of basophilic material, at times to the point where mucin-filled cystic spaces displaced the residual elements of the media. Early in the course of the study this relation seemed so constant that additional sections were taken whenever mucin could not be demon-

TABLE 6.—*Medial Vascularization in Relation to Degree of Sclerosis in Cases of Dissecting Aneurysm of Aorta*

Degree of Medial Vascularization	Cases in Which Given Degree of Intimal Sclerosis Was Observed				
	Mild	Moderate	Marked	None	Total
Mild	3	2	2	7	14
Moderate	8	15	15	6	44
Severe	1	6	5	1	13
None	0	0	0	0	0
Total	12	23	22	14	71

strated. There can be no doubt, however, that primary degeneration of the elastica may occur without the accumulation of chromatrophic substance.

Reticulum fibers, which normally surrounded the elastic fibers like a sleeve, disappeared simultaneously with them. Early phases of disintegration other than focal loss of stainability were not observed.

The muscle component of the media participated only passively in degeneration of the elastic type. The orderly circumferential orientation of the muscle fibers was disturbed. Frequently the fibers were found in small clusters and islets separated from neighboring muscle bundles by wide bands of mucoid material and myxomatous tissue. Such fibers, having lost their insertions (the elastic laminae), were frequently retracted and plump (Fig. 7). Regenerative activity of muscle was not observed.

Medial Vascularization.—Noted consistently, but not emphasized by other investigators, was medial vascularization, which accompanied degeneration of either type. The vessels were thin-walled and widely patent, supported essentially by the substance of the surrounding defective media. Structurally neither arterial nor venous characteristics could be recognized. From the adventitia, these vessels rarely penetrated beyond the middle third of the media. Usually they were accompanied by infiltrating lymphoid cells to only a minimal or slight extent, but occasionally the inflammatory character was more distinct, resulting in a histologic picture strongly suggestive of syphilis, although such an impression drew no support

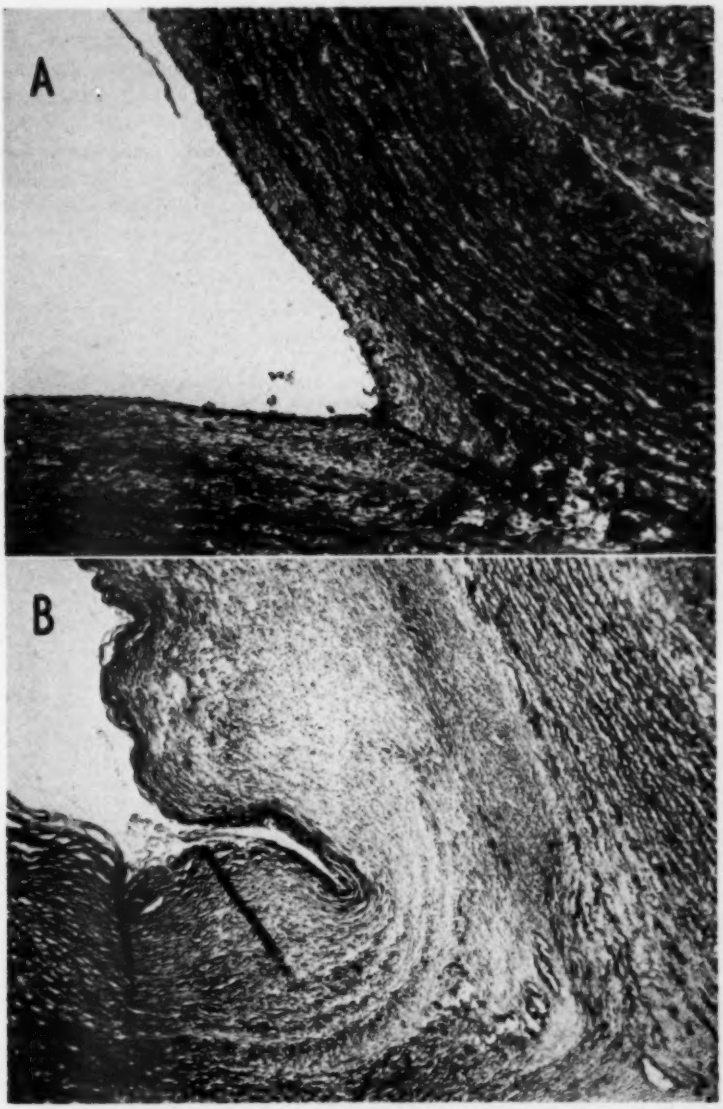

Fig. 8.—*A*, endothelization of the false channel in a dissecting aortic aneurysm. AFIP Acc. 75815, Neg. 104284. Hematoxylin and eosin stain; × 91.

B, thickening and sclerosis of the endothelized lining of the false channel in dissecting aortic aneurysm. AFIP Acc. 74402, Neg. 104282. Hematoxylin and eosin stain; × 48.

from the clinical and anatomic features. Arteriosclerosis was common and was associated with increased vascularity (Winternitz, Thomas, and Le Compte[19]). Table 6 confirms this observation but demonstrates also that significant vascularization occurred in each of 14 individuals without appreciable intimal disease. In assaying this relationship we discounted vascularization incident to an adventitial reaction to hemorrhage.

Evidences of Healing.—No instances of true healing were noted in this series. Although healing has been reported occasionally in the literature, it must be uncommon in the presence of any significant degree of dissection. In the few who survived the dissecting hemorrhage for an adequate interval the false passage became endothelized. As the literature describes,[19] the new-formed intima is susceptible to, and frequently exhibits, sclerosis (Fig. 8*A* and *B*). An adventitial reaction overlying the intramural lesion was common. Its character varied according to the duration of the process before death. An exudative leucocytic response was associated

TABLE 7.—*Age in Relation to Type of Medial Degeneration in Cases of Dissecting Aneurysm of Aorta*

Age Group	Cases in Which Stated Type of Degeneration Was Observed			
	Primarily Elastic	Primarily Muscle	Co-existent	Total
Under 20	1	..	..	1
20-29	13	2	2	17
30-39	2	3	4	9
40-49	..	4	6	10
50-59	..	11	7	18
60-69	..	11	1	12
70-79	..	3	..	3
80-89	..	2	..	2
Total	16	36	20	72

with symptoms of a few hours' duration. Survival beyond one or two days permitted the progressive development of a productive inflammatory process which culminated in fibrosis and scarring. It is undoubtedly the reinforcement of a weakened aortic wall by such a process that allows prolonged survival. In a number of instances in which an exudative or early productive adventitial response was observed, the presence of definite fibrosis or scarring, in addition, led to the inference that the degenerative medial process was much older than the dissecting aneurysm.

ETIOLOGY AND PATHOGENESIS

The cause of the medial degenerative process is obscure, and the condition fully deserves the frequently used designation "idiopathic." It is apparent that the degenerative process of the elastic type must be explained on a basis different from that of the muscle type. Not only are the two histologically distinct, but they also involve different age groups. If the type of medial degeneration is plotted against the age, as in Table 7, it is noted that the younger group exhibits the elastic type; the older, involvement of the muscle, and the intermediate, a combination of muscle and elastic types.

19. Winternitz, M. C.; Thomas, R. M., and Le Compte, O. M.: The Biology of Arteriosclerosis, Springfield, Ill., Charles C Thomas, Publisher, 1938.

Degenerative lesions of the aortic media of the types described have been demonstrated to be more frequent and extensive proximally than distally. There is a similar gradation in the mechanical stress to which the vessel is subject and presumably in the metabolic activities essential to the maintenance of vascular integrity. A structural breakdown resulting from a systemically effective process would occur first and most extensively at the sites of greatest metabolic activity. Duff's [20] observation of the greater destructive effect of diphtheria toxin on the proximal aorta of experimental animals seems pertinent to this point. Obviously, however, the etiology of the human disease is much more complex.

Congenital Anomalies.—Congenital anomalies, principally cardiovascular (Table 8), were unusually frequent, especially in the younger age group in which medial degeneration of the elastic tissue type predominated. The significance of such a high proportion of malformation is considered at length elsewhere.[21] Suffice it to say that the evidence reviewed leads to the suspicion that the primary defect

TABLE 8.—*Congenital Anomalies in Eighty-Five Cases of Dissecting Aneurysm of Aorta*

	Cases
Bicuspid aortic valve	8
Coaretation of aorta	3
Coaretation of aorta and arachnodactyly	1
Bicuspid aortic valve and coaretation of aorta	1
Bicuspid aortic valve and aberrant renal artery	1
Bicuspid aortic valve and absent coronary artery	1
Others	
Patent ductus arteriosus	2
Arachnodactyly	2
Patent interauricular septum (7 by 7 mm.) and Meckel's diverticulum	1
Abnormal tricuspid valve ("5 leaflets")	1
Accessory pulmonary lobe	1
Horseshoe kidney	1
Hypoplastic kidney	1
Cases with anomalies	24
Total anomalies	29

may be biochemical or metabolic rather than morphologic in nature. Furthermore, the fact that anatomic lesions appear and develop long after birth suggests that the metabolic deficiency resides in an inferior and more vulnerable mechanism for the maintenance of elastic tissue integrity rather than in one which is entirely inadequate. There is considerable variation in the age at which the anatomic lesion may appear, and one must assume either a commensurate variation in the severity of the defect or the operation of other interfering factors, or both.

Role of Senility in the Degenerative Process.—Morphologically it is not possible to distinguish the muscle variety of medial degeneration in dissecting aneurysm from the one which accompanies aging. Degeneration of the muscle component, occurring predominantly in the older age group, may be a manifestation of senility or of physiologic "wear and tear." The variability of the age at which it appears

20. Duff, G. L.: Medial Degeneration in Aorta of Rabbit Produced by Diphtheria Toxin, Arch. Path. **13**:543-557 (April) 1932.

21. Gore, I.: Dissecting Aneurysms of the Aorta in Individuals Under the Age of 40, to be published.

would then reflect only individual differences (genetic?) in durability. Myers and Lang [22] have shown chemically that aging is associated with a progressive diminution of both muscle and elastic components of the aortic wall. Erdheim [23] and Cellina [24] described foci of muscle atrophy in the middle and outer layers of the media of senescent individuals. The latter found focal loss of muscle in 9 of 10 aortas from individuals over 72 years of age who had only minimal arteriosclerosis. It is evident that when muscle depletion is minor and is limited to small foci, sufficient reserve remains in the aortic wall to preclude any significant consequence (though this may be one of the factors contributing to the gradual dilatation of the aorta with age). It is equally apparent that the opposite is also true, that with extensive muscle depletion the strain of even ordinary physiologic activity may be sufficient to lead to rupture of the otherwise unaltered elastic laminae. This essentially mechanical failure is clearly a secondary occurrence and is to be distinguished from primary disease of the elastica. In other tissues and organs, too, generalized atrophy has long been considered a manifestation of senility. In aortas exhibiting dissecting aneurysm, then, the lesion would differ only quantitatively from the degenerative changes considered within the limits of tolerance for that age group. Such an explanation should not distract the investigator from seeking more fundamental information regarding the intrinsic metabolism of smooth muscle and its relation to aging, information which would permit a better insight into the nature of the lesion. Morphologic degenerative changes in the elastica accompanying aging described by Hass [25] are not similar to the medial lesion under consideration.

Systemic Factors Affecting the Integrity of the Media.—Holman and his coworkers [26] have produced inflammatory lesions of the aorta and other vascular structures in dogs by the complementary action of a lipid dietary factor and renal injuries induced by various methods. Although the experimental lesions are not comparable with idiopathic medionecrosis in man, they illustrate the combined action of two factors, either of which alone is ineffectual. The experimental work also demonstrates the influence and importance of calorically insignificant dietary factors in maintaining the integrity of vascular structures.

Other factors have been shown to be capable of affecting adversely the structure of the media. Wiesel [27] described degenerative changes involving the muscle and

22. Myers, V. C., and Lang, W. W.: Some Chemical Changes in the Human Thoracic Aorta Accompanying the Aging Process, J. Gerontol. **1**:441-444, 1946.

23. Erdheim, J.: (*a*) Medionecrosis aortae idiopathica, Arch. path Anat. **273**:454-479, 1929; (*b*) Medionecrosis aortae idiopathica cystica, ibid. **276**:187-229, 1930.

24. Cellina, M.: Medionecrosis Disseminata Aortae, Arch. path. Anat. **280**:65-86, 1931.

25. Hass, G. M.: Elastic Tissue: III. Relations Between the Structure of Aging Aorta and the Properties of the Isolated Aortic Elastic Tissues, Arch. Path. **35**:29-45 (Jan.) 1943.

26. Holman, R. L.: Acute Necrotizing Arteritis, Aortitis and Auriculitis Following Uranium Nitrate Injury in Dogs with Altered Plasma Proteins, Am. J. Path. **17**:359-376, 1941; Necrotizing Arteritis in Dogs Related to Diet and Renal Insufficiency: Evidence for a Dietary Factor, ibid. **19**:977-991, 1943. Prevention of Experimental Arteritis in Dogs by Vitamin E, Proc. Soc. Exper. Biol. & Med. **55**:307-309, 1947. Holman, R. L., and Swanton, M. C.: "Dietary Factor" in Necrotizing Arteries in Dogs a Lipid Substance, ibid. **63**:87-89, 1946.

27. Wiesel, J.: Die Erkrankungen arterieller Gefässe in Verlaufe akuter Infectionen: II, Ztschr. Heilk. **7**:262-294, 1906; III., ibid. **8**:69-100, 1907.

elastic elements of the arterial media following various acute infectious diseases. However, these effects in themselves seem to have little in common with idiopathic medionecrosis. This view is well expressed by Klotz and Simpson [28]:

> . . . Admitting that certain bacterial toxins may cause medial degenerations and necroses, it is far from clear how these processes become progressive and appear in their advanced form many years after the infectious process. Nor do the ruptures of the aorta appear only in those individuals who have suffered unusual frequency or severe grades of infectious disease.

Erdheim,[22] too, was inclined to doubt that infectious processes played a significant role in the pathogenesis of idiopathic medial degeneration. He proposed an etiologic role for epinephrine, however, much as Gsell [29] had for nicotine. If this were correct, a significantly greater incidence of medionecrosis would be apparent among chronic asthmatics who take epinephrine or epinephrine-like substances regularly than among the general population, but we are not aware of any report of such an observation. Hueper [30] is of the opinion that bacterial toxins, as well as epinephrine, nicotine, and other vasotonic substances of endogenous and exogenous origin, produce medial lesions by local anoxemia. The way in which the anoxemia is brought about varies considerably. It may result from vasospasm as well as vasoparesis, from hypertonia as well as hypotonia. It does not seem reasonable to assume that provision of an adequate oxygen supply to the aortic wall is the only important factor assuring structural normality.

Vascularization of the Media as a Contributing Factor.—As previously mentioned, increased medial vascularity and slight inflammatory infiltration have been observed by other investigators, most of whom minimized them in emphasizing the primary medial degeneration. It would be a unique degenerative process indeed that did not incite some degree of reparative reaction, secondary, it is true, but deserving emphasis in its own right because it is of key importance to the initiation of dissection. Its significance may, perhaps, be best illustrated by comparing the process with that occurring in syphilitic aortitis. In the latter there is characteristically an increase in the vasa vasorum. There is also focal destruction of the elastic and muscle components of the media; yet dissecting aneurysm is a rare complication. But in syphilitic aortitis the inflammatory process is violent. The vasa exhibit endarteritis which narrows and obstructs their lumina, accompanied by a prominent perivascular inflammatory infiltrate, which to some extent, at least, reinforces their walls. Fibrosis, which appears with chronicity and involution, augments this effect and serves also to knit together the remnants of the damaged laminae.[31] In contrast, the inflammatory process, if it may be so characterized in medial degeneration, is mild. The vasa are thin-walled, widely patent, unaffected by endarteritis, and are supported by very defective aortic media. Such vessels are highly vulnerable to rupture, and should it occur, intramural hemorrhage would result. The tension to which such an extravasate is subject within the aortic wall

28. Klotz, O., and Simpson, W.: Spontaneous Rupture of the Aorta, Am. J. M. Sc. **184**:455-473, 1932.

29. Gsell, O.: Wandnekrosen der Aorta als selbständige Erkrankung und ihre Beziehung zur Spontanruptur, Arch. path. Anat. **270**:1-36, 1928.

30. Hueper, W. C.: Arteriosclerosis: A General Review, Arch. Path. **38**:162-181 (Sept.) and 245 (Oct.) 1944; **39**:117-131 (Feb.) 1945.

31. Weiss.[10] Klotz and Simpson.[28]

contributes to its tendency to spread. Inasmuch as a few dissecting aneurysms are entirely limited to the media and have no intimal or external communications, we infer that they must have originated in this fashion.[32] By inference again, the ruptured vessel must be arterial in nature to provide the force for dissection; the pressure of venous blood in the thorax under physiologic circumstances is negative. The more usual variety of aneurysm results when such an intramural hemorrhage ruptures secondarily into the lumen. Depending on the condition of the overlying layers, the secondary rupture may occur promptly or not until the disruption of the blood supply to that portion of the vessel wall by the medial hematoma produces sufficient additional weakening. In either event, penetration of the intima admits pulsating blood at maximum arterial pressure to the weakened media and provides the *vis a tergo* for rapid dissection. The latter, as a rule, proceeds distally, but the underlying basic lesion clearly explains instances of so-called proximal dissection. As Shennan [1] has pointed out, some degree of proximal dissection is almost invariable; extensive proximal dissection occurred in 25 (of 300) collected cases, and the dissection was wholly proximal in 5. In the present series proximal dissection occurred in 18%. With prolongation of the survival time, such centripetal extension becomes more commonplace, and Shennan found it in nearly half of the cases of old dissecting aneurysm he collected.

Intramural hemorrhage does not invariably result in dissection. With medial degeneration of limited extent, it remains local and undergoes involution to form lesions of two types. The first was characterized by abrupt localized destruction of the entire thickness of the media, with fibrous tissue replacement directly contiguous to a thickened adventitia. Only vestiges of the elastica remained to indicate the site of the media. The lesion, identical with that reported by Gallavardin and Gravier [33] and Peery [34] as "incomplete rupture of the aorta," was described and illustrated by Eppinger [35] in 1887 as a healed rupture. The second and more frequent type involved the inner half of the media rather than the overlying intima. Resorption of a hematoma evidently occurs less readily at such a site, relatively remote from the adventitia, than it does in the first type. Hence this lesion is characterized by the presence of the degenerated blood and cholesterol material which it releases. A granulomatous response was observed in the immediately surrounding tissues. When such a lesion involves the intima so that media is fused with intima, it may aggravate an already existing atherosclerotic process (Fig. 9), but how often this occurs is conjectural, since all that is available for examination is the specimen representing the end-stage. It should be considered, however, where there is an abrupt defect in the media rather than the more gradual compression which is characteristic of the intimal disease.

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32. Gore, I.: Pathogenesis of Dissecting Aneurysm of the Aorta, to be published.

33. Gallavardin, L., and Gravier, L.: Rupture incomplète de l'aorte: Insuffisance aortique fonctionnelle consécutive, Paris méd. **45**:23-26, 1922.

34. Perry, T. M.: Incomplete Rupture of the Aorta: A Heretofore Unrecognized Stage of Dissecting Aneurysm and a Cause of Cardiac Pain and Cardiac Murmurs, Arch. Int. Med. **70**:689-713 (Nov.) 1942.

35. Eppinger, H.: Pathogenesis (Histogenesis und Aetiologie) der Aneurysmen einschliesslich des Aneurysma equi verminosum, Berlin, A. Hirschwald, 1887

Role of Hypertension.—The great resistance of the normal aortic wall to bursting and tearing has been shown repeatedly.[36] Hypertension, therefore, cannot adequately explain dissecting aneurysm, but our findings do shed light on the significance of increased arterial pressure, which is so often observed clinically. In this series (see Table 2) elevated blood pressure was present in 58%. It affected only 25% of individuals under 40 years of age, even when simple systolic hypertension was included, in comparison with 85% of the patients who were 40 years of age or older. Considering again the histologic picture and that dissection is

Fig. 9.—The aortic media is interrupted by an amorphous mass of eosinophilic material rich in cholesterol. AFIP Acc. 54825, Neg. 104279. Hematoxylin and eosin stain; × 90.

essentially an accident in a fairly common process,[37] one might reasonably expect rupture of an unsupported thin-walled arterial vessel more frequently among hypertensive than among normotensive individuals. It seems likely, too, that the transient hypertension which accompanies physical or emotional stress might be significant.

36. (*a*) Moritz, A. R.: Medionecrosis Aortae Idiopathica Cystica, Am. J. Path. **8**:717-734, 1932. (*b*) Robertson, J. S., and Smith, K. V.: An Analysis of Certain Factors Associated with the Production of Experimental Dissection of the Aortic Media, in Relation to the Pathogenesis of Dissecting Aneurysm, J. Path. & Bact. **60**:43-49, 1948. Klotz and Simpson.[29]

37. Rottino, A.: Medial Degeneration in a Nonruptured Aorta Appearing Syphilitic Macroscopically, Arch. Path. **27**:320-327 (Feb.) 1939.

In some respects, at least, the process has an analogue in cerebral apoplexy. In each instance the elevated blood pressure merely exploits the structural weakness of primarily diseased or abnormal vessels. It would seem reasonable to infer that hypertension also acts in another fashion, for the additional burden it creates would accelerate the progress of a degenerative process already initiated.

Nature of the Mucoid Substance.—Considerable emphasis has been attached to the intramedial accumulation of mucoid (chromatrophic) material.[38] Erdheim [23b] had expressed the frequently cited opinion [39] that the accumulated mucoid material represents the initial lesion which precedes the focal loss of elastic and collagenous tissue. Cellina,[24] on the contrary, considered that there is a primary injury of the elastica and that the mucoid material appears as a degenerative product. Gsell,[29] also, concluded that this material was secondary to a medial degenerative injury (muscle) but recognized further that it was loose collagenous tissue, part of a reparative reaction. It seems likely, too, that this tissue plays a part in the structural development of the aorta, since it has been noted in abundance in the vessels of young embryos.[40] Its occurrence in association with congenital vascular anomalies [41] also implies a role in embryologic development. The appearance of this material is not limited to embryologic development and disturbances, for Schultz [42] has noted progressive increase of chromatrophic substance with aging. It seems, moreover, that the increase is probably proportionate to the reduction of elastic and muscle fibers.[43] In idiopathic medial degeneration there is a quantitatively variable and inconsistent relation between the loss of tissue structure and the accumulation of myxomatous or mucoid material. In no instance was chromatrophic substance observed in the absence of medial degeneration, whereas the converse was true; and accordingly the appearance of mucin, on this basis alone, warrants considering it a reactive phenomenon. Its accumulation in cysts seems merely a consequence of the arterial tension to which the aortic wall is subject. Under the impetus of the hydrostatic pressure the semifluid material is propelled within the structure of the weakened media to points of least resistance, frequently foci in which several adjacent elastic laminae have been lost. Obvious compression and distortion of the residual undamaged lamellae by the cyst contents, therefore, need not be regarded as an index of excessive primary "local-production" in the sense that Erdheim [23] proposed. The persistence of the elastic laminae appears to explain adequately the failure to find cystic accumulations in the muscle variety of medial disease.

Distribution of Lesions.—Although the changes we have described may occur in any portion of the aorta, the frequency with which they occur proximally serves

38. Kountz, W. B., and Hempelmann, L. H.: Chromatrophic Degeneration and Rupture of the Aorta Following Thyroidectomy in Cases of Hypertension, Am. Heart J. **20**:599-610, 1940.

39. Roberts, J. T.: Medionecrosis Aortae Idiopathica Cystica: A Report of Case with "Healed" Dissecting Aneurysm, Am. Heart J. **18**:188-200, 1939. Moore, R. A.: Textbook of Pathology, Philadelphia, W. B. Saunders Company, 1944. Moritz.[36a]

40. Costa-Florenz, A. von: 1. Normale und pathologische Anatomie, Ztschr. Kreislaufforsch. **23**:715-717, 1931.

41. Harrison, F. F.: Coarctation of the Aorta of the Adult Type, Associated with Cystic Degeneration of the Media in the First Portion of the Arch, Arch. Path. **27**:742-747 (April) 1939.

42. Schultz, A.: Pathologie der Blutgefässe, Ergebn. allg. Path. u. path. Anat. (Abt. 1) **22**:207-349, 1927.

43. Björling, E.: Über mukoides Bindegewebe, Arch. path. Anat. **205**:71-88, 1911.

to explain the greater localization of intimal tears in that segment. There are also mechanical factors which contribute. Not only is there greater hydrostatic pressure but the tissues of the arch must sustain the additional stress required to change the direction of the blood stream from cephalic to caudal. The pulsatile character of the circulation produces repeated transverse as well as longitudinal stresses. Shennan [1] emphasized points of particular stress just above and below the right pulmonary artery which braces the aorta as it passes posteriorly, and also the site of the ligamentum arteriosum arteriae pulmonalis where the relatively mobile arch merges with the fixed descending aorta.

SUMMARY

A series of 85 cases of dissecting aortic aneurysm collected at the Armed Forces Institute of Pathology furnished the material for pathologic study of this lesion. The gross pathologic features were identical with those recounted in numerous descriptions in the literature. There was preponderant involvement of the proximal segments of the aorta. Hemorrhage was the usual cause of death, but there were 16 cases in which it did not occur. In 11 instances the dissection had become rechanneled, and in 6 others there were no intimal breaks or tears. In 7 cases a true aneurysmal swelling of the proximal part of the aorta had preceded the terminal dissection.

Microscopically, a degenerative process was demonstrated in the aortic media in all cases, and it was impossible to distinguish between so-called spontaneous rupture and the more usual type of dissecting aneurysm. The elastic laminae were affected primarily in the younger individuals. In the older age groups the changes were predominantly in smooth muscle. Lesions of both types were present at intermediate ages but were not always coextensive; thus the two processes were regarded as independent, possibly entailing different etiologic mechanisms. However, in all cases the weakened area in the aortic wall contained increased numbers of thin-walled vasa and a slight but variable inflammatory reaction. The basophilic-staining material, actually myxomatous tissue, was frequently abundant in degeneration of the elastic type. These features, together with a frequent productive adventitial reaction which antedated the hemorrhage, were regarded as constituting the reparative reaction to the initial medial degeneration.

An unusually high incidence of developmental anomalies in the younger age groups pointed to a congenital factor in this form of the disease, at least. Changes accompanying senescence may explain others. In either event, it seems likely that a biochemical or a metabolic defect preceded the morphologic one, and if this supposition can be confirmed, the reason for the greater frequency of lesions in proximal segments of the aorta becomes apparent. It is not so much a matter of the "chain breaking at the weakest link" as it is the disproportion in the load to which each link is subject. Mechanical factors are probably influential, too, in initiating the intramural hemorrhage and the secondary intimal tear. Intimal disease plays no appreciable role in this condition. Hypertension, although not etiologically significant, plays an important secondary role.

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PATHOGENESIS OF DISSECTING ANEURYSM OF THE AORTA

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DETROIT

DISAGREEMENT regarding the pathogenesis of dissecting aneurysm of the aorta still exists, even though the lesion has been recognized by that name since 1826, when it was first applied by Laennec.[1] Intimal disease, considered essential to its development by Laennec,[1a] MacCallum,[2] and others, is no longer so regarded. Most of the current textbooks, reflecting the experience that has accumulated with time, concede the importance of primary medial degeneration.[3] Whether an intimal break is necessary to establish hemorrhagic dissection of the media and whether hypertension is of etiologic importance appear to be the principal issues.

INTIMAL RUPTURE IN DISSECTING ANEURYSM OF THE AORTA

A primary intimal break seems to have been suggested to some investigators [4] by the orientation so frequently taken by the laceration. The transverse direction commonly observed does indeed suggest a longitudinal tearing force, but the additional inference that the intima ruptures from within the lumen outward rather than in the opposite direction is scarcely reasonable. Holland and Bayley have previously attempted to explain variations in the direction of the tear in different portions of the aorta *solely* as a function of the prevailing major longitudinal or

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or the policy of the Veterans Administration.

1. (*a*) Laennec, R. T. H.: Traité de l'ausculation médiate et des maladies des poumons et du cœur, ed. 2, Paris, J. S. Chaudé, 1826. (*b*) Sherman, T.: Dissecting Aneurysms, Medical Research Council, Special Report Series, No. 193, London, His Majesty's Stationery Office, 1934.

2. MacCallum, W. G.: Dissecting Aneurysm, Bull. Johns Hopkins Hosp. **20**:9-12, 1909.

3. Moore, R. A. A Textbook of Pathology, Philadelphia, W. B. Saunders Company, 1944, pp. 989-992. Hall, E. M.: The Blood and Lymphatic Vessels, in Anderson, W. A. D., editor: Pathology, St. Louis, C. V. Mosby Company, 1948, pp. 593-598. Karsner, H. T.: Human Pathology, ed. 7, Philadelphia, J. B. Lippincott Company, 1949, pp. 433-435. Boyd, W.: The Pathology of Internal Disease, ed. 4, Philadelphia, Lea & Febiger, 1944, pp. 125-127.

4. (*a*) Holland, L. F., and Bayley, R. H.: Dissecting Aneurysm: A Report of 19 Cases, with a Review of the Recent American Literature, Am. Heart J. **20**:223-235, 1940. (*b*) Peery, T. M.: Incomplete Rupture of the Aorta: A Heretofore Unrecognized Stage of Dissecting Aneurysms and Cause of Cardiac Pain and Cardiac Murmurs, Arch. Int. Med. **70**:689-713 (Nov.) 1942. (*c*) Moritz, A. R.: Medionecrosis Aortae Idiopathica Cystica, Am. J. Path. **8**: 717-734, 1932.

transverse stress, but a study of dissecting aneurysms in young individuals indicates a more significant factor to be the degree of preservation of the medial elastic laminae.[5]

Three of the five cases of dissecting aneurysm reported by Tyson [6] in 1931 were without intimal rupture, leading him to propose, as Krukenberg [7] had before him, that the initial lesion was an intramural hematoma caused by rhexis of one of the vasa vasorum in a focus of medial weakening. Similar instances have been accumulating in the medical literature and constitute one of the most potent arguments against the essentiality of an initial intimal tear (Table). As a matter of fact, such a frequent intimal defect as arteriosclerotic ulceration rarely leads to dissection, although local hemorrhagic infiltration is commonly observed.[8] In the usual form of dissecting aneurysm an internal tear localized at the site of an atherosclerotic plaque is infrequent [8] despite the prevalence of severe intimal disease. Peery [4b] described the condition known as incomplete rupture of the aorta, both the isolated

Dissecting Aneurysms Without Intimal Rupture

Author	Year	Cases
Krukenberg [7]	1920 (inferior thyroid art.)	1
Tyson [6]	1931	3
Fahr, T., in Aschoff, L.: Pathologische Anatomie, ed. 8, Jena, Gustav Fischer, 1936, Vol. 2; cited by Sailer [8b]	1936	1
Hamburger, M., Jr., and Ferris, E. B., Jr.: Dissecting Aneurysm: A Study of 6 Recent Cases, Am. Heart J. **16**:1-13, 1938	1938	2
Reisinger, J. A.: Dissecting Aneurysm of the Aorta, Arch. Int. Med. **65**:1097-1115 (June) 1940	1940	1
Mote, C. D., and Carr, J. L.: Dissecting Aneurysm of the Aorta, Am. Heart J. **24**:69-87, 1942	1942	6
Blain, A., III; Glynn, T. P., and Hiratzka, T.: Dissecting Aorta Aneurysm Involving a Renal Artery and Simulating Acute Nephrolithiasis, J. Urol. **53**:753-761, 1945	1945	1
Blain, A., III: Dissecting Aortic Aneurysms Without Intimal Rupture: A Note on Pathogenesis of Dissecting Aneurysms, Univ. Hosp. Bull., Ann Arbor **13**:21-24, 1947	1947	1
Bauersfeld, S. R.: Dissecting Aneurysm of the Aorta: A Presentation of 15 Cases and a Review of the Recent Literature, Ann. Int. Med. **26**:873-889, 1947	1947	1
Gore and Seiwert [8c]	....	6
	Total	23

form and that associated with fatal dissecting aneurysm, of which he considers it a precursor. If his interpretation of the lesion as a primary intimal tear produced by hypertension is correct, it provides an example of failure of an intimal break to result in dissection, even though that process may ensue in another segment of the same aorta. The microscopic structure, however, suggests the alternative explanation that the intima remains intact but is forced by arterial pressure into an abrupt depression formed by a primary medial defect.[8c] It will be recalled that the aneurysm and the linear intimal wrinkling which are looked on as characteristic of syphilis but which also occur in idiopathic medionecrosis are actually the results

5. Gore, I.: Dissecting Aneurysms of the Aorta in Individuals Under the Age of 40, to be published.

6. Tyson, M. D.: Dissecting Aneurysms, Am. J. Path. **7**:581-603, 1931.

7. Krukenberg, E.: Beiträge zur Frage des Aneurysma dissecans, Beitr. path. Anat. **67**: 329-351, 1920.

8. (*a*) Klotz, O., and Simpson, W.: Spontaneous Rupture of the Aorta, Am. J. M. Sc. **184**:455-473, 1932. (*b*) Sailer, S.: Dissecting Aneurysm of the Aorta, Arch. Path. **33**:704-730 (May) 1942. (*c*) Gore, I., and Seiwert, V. J.: Dissecting Aneurysm of the Aorta: Pathologic Aspects; an Analysis of 85 Fatal Cases, Arch. Path., this issue, p. 121. Shennan.[1b]

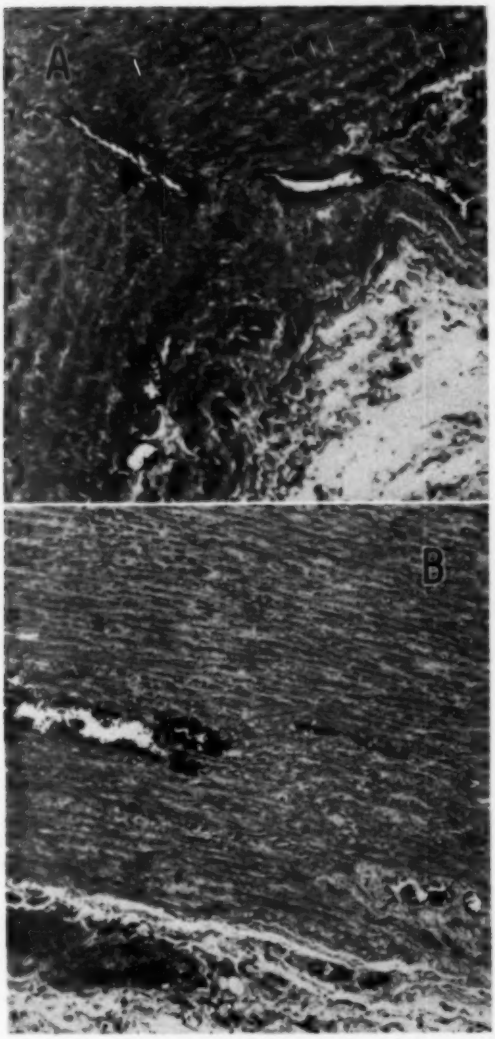

Fig. 1.—*A*, vasa vasorum penetrating the media of an aorta which in other foci exhibits considerable medial degeneration. Armed Forces Institute of Pathology (AFIP) Negative 106130; hematoxylin and eosin stain; × 315.

B, cleft partially splitting the aortic media at the junction of the middle and outer thirds. Blood escaping from vasa vasorum into the weakened area is regarded as an early phase of dissecting aneurysm. AFIP Neg. 79691—1; hematoxylin and eosin stain; × 50.

of passive adaptation of the intact aortic lining to defects in the underlying media. Incomplete rupture differs only in its position, its sharp delineation, and the abruptness of its appearance, to judge from the associated clinical symptoms. In this sense it represents a special variant of dissecting aneurysm rather than an essential stage in its development. It differs from the more frequent form of the disease only in the superficial position and limited extent of the medial fault. It is indicative of medial degeneration in an aorta, and, as Peery [4b] observed, it is often followed by true and fatal dissections in other portions of the vessel.

Fig. 2.—Advancing edge of an intramural aortic hemorrhage in a dissecting aneurysm. Observe the abundance of myxomatous material and the gaps in some of the elastic laminae. AFIP Accession 51691, Neg. 104274; hematoxylin and eosin stain; × 315.

ROLE OF MEDIAL DEGENERATION IN DISSECTING ANEURYSM OF THE AORTA

Recent histologic studies of the aorta in 72 cases of dissecting aneurysm at the Armed Forces Institute of Pathology [9] yielded information which seems to provide the basis for a better understanding of the pathogenesis of the condition. Medial degeneration was found to be present in each instance, although it varied considerably in extent and severity. Microscopically, three variants of the process were observed. The first, which was most frequent in patients under 40, involved the elastic laminae and was frequently associated with increased quantities of basophilic ground substance or myxomatous material, often accumulated in cyst-like spaces compressing residual intact lamellae. A more common form, affecting an

9. Gore.[5] Gore and Seiwert.[8c]

older age group,[9] involved the smooth muscle of the aortic media. It could be recognized as a pale focus in which the intact concentric elastic laminae had lost their normal sinuosity, as though they had been overstretched and lay more closely approximated than usual. The third form combined the features of the other two and was usually observed in the age group between those in which one type predominated. It will be recalled that the medial lesion described by Erdheim [10] corresponds best to the first variant described, whereas the involvement of the medial musculature in the second is similar to the lesion described by Gsell.[11] No evidence

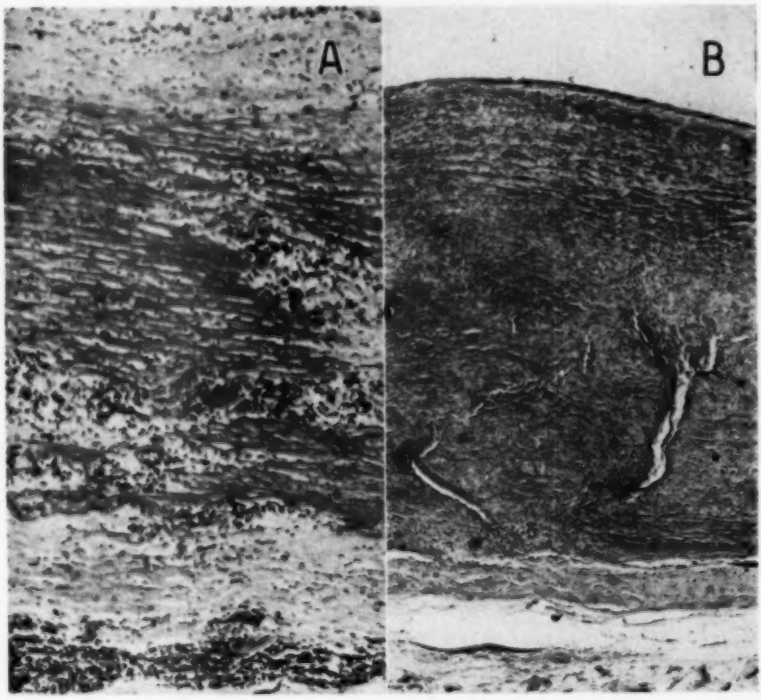

Fig. 3.—*A*, aortic wall from the vicinity of a dissecting aneurysm. The inflammatory reaction and the adventitial scarring are more conspicuous than usual. In such a field it would be impossible to rule out syphilis without recourse to clinical and to other autopsy evidence. Observe the ischemic necrosis of portions of the media. AFIP Neg. 207601—2; hematoxylin and eosin stain; × 60.

B, aortic wall in which the outer media has been replaced focally by scar tissue. Note the adventitial fibrosis, the conspicuous thin-walled vasa, and the sparse inflammatory infiltrate.

was found which supports the contention of either of these authors that the lesion described by him was primary and a necessary prelude to the development of the

10. Erdheim, J.: Medionecrosis aortae idiopathica, Arch. path. Anat. **273**:454-479, 1929; **276**:187-229, 1930.

11. Gsell, O.: Wandnekrosen der Aorta als selbständige Erkrankung und ihre Beziehung zur Spontanruptur, Arch. path. Anat. **270**:1-36, 1928.

other. The distinct impression derived was that the two forms were independent and involved different mechanisms of formation, although the body reacted to each of them in the same manner.

In a number of instances observation of small extravasates of blood about thin-walled vessels lying in foci of medial degeneration remote from the dissecting aneurysm suggested, as it had to others, that medial hemorrhage might constitute the precipitating but not primary event in dissecting aneurysm (Figs. 1 and 2). Indeed, the microscopic evidence indicated that this might be the usual rather than an uncommon mechanism of hemorrhagic dissection. All observations were made as far as possible in portions of the aorta not involved by the dissecting hemorrhage, so that the changes could not be interpreted as a reaction to it. The uniformity of the histologic manifestations both in cases of sudden death and in cases of prolonged survival also argues against a reaction to hemorrhage. Without exception, all aortas in this series showed increased medial vascularization of variable degree, often associated with a rather mild perivascular infiltrate of lymphocytes and a few plasmacytes. The vessels were thin-walled and widely patent; in no instance was endothelial hyperplasia or endarteritis observed. Since vascularity and perivascular infiltration of the media are regarded as cardinal histologic features of syphilitic aortitis, it is pertinent to mention that clinical and pathologic evidence of vascular syphilis was present in only 1 of the 72 cases. Morphologically, when medial degeneration is accompanied by pronounced medial vascularization, it is virtually impossible to distinguish the process from a syphilitic one (Fig. 3*A*). In general, however, the latter shows a much more violent inflammatory reaction plus endarteritis and fibrosis.

COMPARISON OF IDIOPATHIC MEDIAL DEGENERATION AND THE SYPHILITIC AORTIC LESION

A comparison of the lesions of dissecting medial degeneration and syphilitic aortitis suggested that in both the vascularization represented a reactive process: in the former, to a relatively slow degeneration of tissues; in the latter, to the presence of Treponema pallidum. The violence of the syphilitic inflammation seals off the vasa with endarteritis, surrounds them with mantles of fibrous tissue and inflammatory cells, and effectively knits the medial defects with scar tissue. The rarity of dissecting hemorrhage due to syphilis is well known.[12] On the other hand, the bland reaction characteristic of the idiopathic degenerative process fails to narrow the vasa, to support them with sheaths of inflammatory tissue, or to bridge the gaps in the media. Instead, the thin-walled vessels lie essentially unsupported in a focus of medial weakening, an appearance suggesting great vulnerability to rhexis. Similar thin-walled and patent medial vasa that develop in relation to the plaques of intimal arteriosclerosis are the source of the local intramural hemorrhages frequently observed in that condition.[13] Therefore, in evaluating vascularization in relation to primary degeneration of the media, vessels in the vicinity of large intimal

12. Weiss, S.: Clinical Course of Spontaneous Dissecting Aneurysm of Aorta, M. Clin. North America **18**:1117-1141, 1935. Tyson.[6] Klotz and Simpson.[9a]

13. Winternitz, M. C.; Thomas, R. M., and Le Compte, P. M.: Studies in the Pathology of Vascular Disease, Am. Heart J. **14**:399-404, 1937. Wartman, W. B.: Occlusion of the Coronary Arteries by Hemorrhage into Their Walls, ibid. **15**:459-470, 1938.

plaques were excluded. However, in a significant number of cases, including the majority of those in which the patient was less than 40 years of age, this source of error did not exist since arteriosclerosis was not appreciable.

SIGNIFICANCE OF THE MYXOMATOUS COMPONENT OF THE DEGENERATIVE LESION

The "mucin" present in the medial lesions, although sometimes conspicuous, is not unique to this disease but, as originally proposed by Gsell,[11] merely represents another manifestation of the body reaction. Mucin, incidentally, is a misnomer for this material, since it contains stellate cells [11] and a very loose delicate fibrillar mesh; actually it is myxomatous tissue (Fig. 2). Occasionally foci of fibroblastic transformation can be observed, indicating the true nature of the material, and this form of repair was also noted by Moritz.[4c] The peculiar nature of this response to irritation probably reflects the limited histologic composition of the arterial media. At any rate, a wide variety of stimuli irritative to arteries (except the more violent types of inflammatory arteritis, with which this condition has nothing in common) produce an increase of "basophilic ground substance." Particular attention to this feature reveals that it is present, though inconstantly, in pulmonary and bronchial arteries in areas of chronic pneumonitis, in gastric vessels in the vicinity of chronic ulcers, and in vessels encompassed by rapidly growing tumor. It has been observed in the acute invasive stage of syphilitic aortitis when organisms swarmed through the tissues. Separation of the muscle fibers of the media by myxomatous material was described and illustrated by Warren and Gates [14] as observed in pulmonary vessels damaged by irradiation. The "angioneurotic edema" of the vessel wall, characterized by Rich and Gregory [15] as the initial phase of the arteritis of hypersensitivity, probably represents a similar accumulation of basophilic material. It seems likely, too, that the homogeneous ground substance seen in the media of medium-sized and small arteries after acute infections, described by Wiesel [16] and Stoerck and Epstein,[17] represents a similar reaction. Hueper,[18] in reference to work done in collaboration with Ichniowski,[19] stated that "mucinoid or plasmatic imbibition and swelling of aortic media" had been observed in dogs dying within 16 hours after induction of histamine shock. Schlichter,[20] who produced an ischemic type of medionecrosis experimentally, noted the accumulation of mucoid material in the bordering and otherwise normal media, preceding fibroblastic organization of the necrotic zone. A similar accumulation

14. Warren, S., and Gates, O.: Radiation Pneumonitis: Experimental and Pathologic Observations, Arch. Path. **30**:440-460 (July) 1940.

15. Rich, A. R., and Gregory, J. E.: Experimental Demonstration That Periarteritis Nodosa Is a Manifestation of Hypersensitivity, Bull. Johns Hopkins Hosp. **72**:65-88, 1943.

16. Wiesel, J.: Die Erkrankungen arteriellen Gefässe im Verlaufe akuter Infektionen, Ztschr. Heilk. **7**:262-294, 1906; **8**:69-100, 1907.

17. Stoerk, O., and Epstein, E.: Über arterielle Gefässveränderungen bei Grippe, Frankfurt. Ztschr. f. Path. **23**:163-190, 1920.

18. Hueper, W. C.: Arteriosclerosis: A General Review, Arch. Path. **38**:162-181 (Sept.) 1944.

19. Hueper, W. C., and Ichniowski, C. T.: Experimental Studies in Cardiovascular Pathology: Late Vascular Reactions of Histamine Shock in Dogs, Am. J. Path. **20**:211-221, 1944.

20. Schlichter, J. G.: Experimental Medionecrosis of the Aorta, Arch. Path. **42**:182-192 (Aug.) 1946.

of ground substance was observed by Rinehart [21] in the aortas of monkeys subjected to pyridoxine deficiency.

Differences in the distribution of the "mucoid" material can be accounted for without assuming that different mechanisms are responsible for its appearance. Elsewhere [8c] it has been observed that medial degenerative lesions of the elastic tissue type are often featured by the accumulation of basophilic ground substance in cystic spaces, which is not the case with lesions limited to the muscle. The loss of elastica is concurrent with disappearance of the reticulum which normally invests each elastic fiber in a sleeve-like fashion and binds it to its neighbors with anastomotic processes. Not only may the myxomatous tissue occupy gaps left by the degenerative process, but under the prevalent arterial tension this semifluid substance also may dissect along lines of weakness resulting from the loss of the anastomotic fibers, accumulating wherever its advance is checked. If this explanation is accepted, the compression and distortion of the residual unaltered media, sometimes so prominent about such cystic accumulations, need not be considered evidence of local overproduction of "mucin," as suggested by Erdheim.[10]

ADVENTITIAL REACTION TO DISSECTING HEMORRHAGE OF THE AORTA

The reaction of the adventitia to the dissecting hemorrhage usually corresponded in both type and degree to the duration of clinical symptoms. When death was prompt little alteration was to be noted, but if death was delayed even for a matter of hours an exudative inflammatory reaction was usually present. Progressively longer survival could be correlated with a productive process, culminating after several weeks in dense fibrous tissue. Even in some cases in which death was almost immediate, however, a process which clearly antedated the clinical symptoms accompanied the usual adventitial reaction in portions of the aorta (Fig. 3*B*). In the absence of pathologic evidence of previous hemorrhage or some other irritative process, this old lesion could be attributed only to the degenerative changes in the overlying media, which also had preceded the dissection. Since such adventitial changes do not always accompany the medial lesions, they are regarded as secondary to them, thus furnishing additional testimony to the reactive nature of many of the histologic changes of this disease. It would be a unique destructive process which failed to incite a bodily response. Indeed the consistency of this response makes it a most helpful guide in distinguishing antemortem from postmortem histologic changes. Idiopathic medial degeneration of the aorta is not an exception to the rule but is peculiar only in that the repair process which it incites is inadequate as compared with the strain to which the structure is subject.

ROLE OF THE VASA VASORUM

The general acceptance of Erdheim's opinion absolving the vasa vasorum of any role in the pathogenesis of dissecting aneurysm has, to a large extent at least, masked or eclipsed previous and even subsequent statements to the contrary. Yet Moriani,[22] in 1910, described an isolated area of medial splitting that was partly

21. Rinehart, J. F., and Greenburg, D.: The Occurrence of Arteriosclerotic Lesions in Pyridoxine Deficient Monkeys, Am. J. Path. **25**:767-768, 1949.

22. Moriani, G.: Über einen Fall von Aneurysma dissecans aortae mit besonderer Berücksichtigung der frischen Rupturen der Aortenmedia, Arch. path. Anat. **202**:283-305, 1910.

filled with blood from rupture of one of the vasa vasorum. He concluded that medial rupture preceded the intimal tear, a concept arrived at independently by Schede [23] (1908) and Babes and Mironescu [24] (1910) and endorsed subsequently by Krukenberg,[7] Whitman and Stein,[25] Tyson,[6] Shennan,[1b] Winternitz and associates [13] and Sailer.[8b] Tschermak,[26] in 1896, had been impressed with new vessel formation and round cell infiltration coincident with the widespread degenerative process in the media, features which were also present in the case of Babes and Mironescu.[24] Summarizing his personal observations, Shennan [1b] found that 9 of 17 cases presented an increased number of vasa, usually with accompanying mononuclear infiltration or with increased connective tissue mantles. Prominence of the vasa and slight round cell infiltration were recorded in three of the six cases reported by Leitch.[27] Although the multiple isolated intramedial hemorrhage observed by Wolff [28] in the greatly dilated aorta of a 12-day-old infant did not seem to be related to vasa, the artery was also the seat of severe elastic tissue degeneration and cyst formation. Degenerative lesions of aortic media are considerably more frequent than dissecting aneurysms.[29] In this respect, significance is attached to the nonsyphilitic medial vascularization and perivascular inflammatory infiltration observed by Ashworth and Haynes [30] in association with retrogressive medial changes in the aortas of patients with hypertension. These authors observed similar changes, less frequently, in normotensive controls.

Tyson,[6] having found obliterative or occlusive changes in the vasa vasorum in three of his five cases, suggested that they explained the medial lesion. Until recently the proposition attracted little attention. Shennan [1b] commented on the slight degree of endarteritis (of aortic vasa vasorum) he had observed in six of his cases. Klotz and Simpson,[8a] who had found a moderate degree of endarteritis in one case, stated that no "direct relation could be established between the distribution of the vasa vasorum and the location of the necrotic process" in any of their five cases. Sailer [8b] assessed the accumulated evidence at the time of his review (1942) as contradictory to the view that degenerative changes in the media may properly be attributed to obstruction or narrowing of the vasa.

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23. Schede, F.: Beiträge zur Aetiologie, Verlauf und Heilung des Aneurysma dissecans der Aorta, Arch. path. Anat. **192**:52-86, 1908.

24. Babes, V., and Mironescu, T.: Ueber dissezierende Arteriitis und Aneurysma dissecans, Beitr. path. Anat. **48**:221-235, 1910.

25. Whitman, R. G., and Stein, H. E.: A Contribution to the Pathogenesis of Dissecting Aneurysms: A Case of Dissecting Mesaortitis Without Dissecting Aneurysm, J. M. Research **44**:579-592, 1924.

26. Tschermak, A.: Aneurysma aortae dissecans mit Ruptur der Art. coronaria dextra und zweizeitigen Durchbruch nach dem Herzbeutal hin: Pericarditis, Arteriitis, Arch. path. Anat. **146**:233-266, 1896.

27. Leitch, W. H.: Dissecting Aneurysm, with Case Reports, Bull. School Med. Univ. Maryland **29**:7-30, 1944.

28. Wolff, K.: Unbekannte Erkrankungen der Säuglingsaorta mit Schwund des elastischen Gewebes, Arch. path. Anat. **285**:369-384, 1932.

29. Weise, W.: Medianekrosen: Eine Untersuchung am laufenden Sektionsmaterial, Beitr. path. Anat. **93**:238-278, 1934. Rottino, A.: Medial Degeneration, Cystic Variety in Unruptured Aortas, Am. Heart J. **19**:330-337, 1940.

30. Ashworth, C. T., and Haynes, D. M.: Lesions in Elastic Arteries Associated with Hypertension, Am. J. Path. **24**:195-209, 1948.

Recently the issue was reopened when Schlichter [20] reported that he had produced medial degeneration experimentally in dogs by cautery devascularization of segments of the aorta. It is doubtful, however, whether such acute ischemic changes can be considered comparable with the lesions of idiopathic medial degeneration. In the latter, viable tissue is present throughout the lesion and is not limited to its margins; furthermore, at least in acute lesions, the "ghost-like" remnants of medial tissues are still present in infarcts, in contrast to the picture in the idiopathic process (Fig. 3*A*). In this study these two features permitted differentiation between primary degenerative lesions and necroses secondary to interruption of the blood supply due to dissecting hemorrhage. Subsequently, in support of their thesis, Amromin, Schlichter, and Solway [31] reported narrowing of adventitial vasa in the aortas of 7 of 12 patients with dissecting aneurysm. Ashworth and Haynes [30] observed an appreciable incidence of hyperplastic and sclerotic change in the adventitial vasa of hypertensive individuals.

Contrary to the observations of Schlichter, Amromin, and Solway,[32] there was nothing in the 72 cases of the present series to indicate that such lesions are more than a reflection of the secondary effects of long-standing hyperpiesis on the entire vascular tree. Thickening and narrowing of adventitial vasa were noted in a few of the hypertensive patients, but the lesions were so infrequent and so minor that it is difficult to regard them as the cause of significant local nutritional changes. The absence of even slight lesions of the vasa in 23 of 26 individuals under the age of 40 years scarcely serves to support the view that the medial lesions present in all of them were the result of ischemia.

ROLE OF HYPERTENSION IN DISSECTING ANEURYSM OF THE AORTA

The frequency of a history of increased arterial pressure in cases of dissecting aneurysm has been and continues to be cited [4b] as evidence of the fundamental etiologic significance of hypertension. However, Shennan [1b] noted a lack of pathologic evidence of preexistent hypertension in 32 of 163 cases (20%). McGeachy and Paullin [33] reported that there was a history of high blood pressure in 60, a history of exertion in 33, and a history of neither high blood pressure nor exertion in 34 (27%) of the 127 cases they had collected. At the time of onset of dissection, Gore and Seiwert,[8c] using both clinical and pathologic criteria, found that in only 58% of 85 patients with dissecting aneurysm was there evidence of previous hypertensive cardiovascular disease, a percentage which corresponds to that arrived at by Baer and Goldburgh.[34] More significantly, there was no record of elevated blood pressure accompanying dissecting aneurysm in 20 of the 26 individuals under the age of 40.[5] Eighty-five per cent of the patients 40 years of age and older were hypertensive. Investigating the question experimentally, Oppenheim,[35] Klotz and

31. Amromin, G. D.; Schlichter, J. G., and Solway, A. J. L.: Medionecrosis of the Aorta, Arch. Path. **46**:380-385 (Oct.) 1948.

32. Schlichter, J. G.; Amromin, G. D., and Solway, A. J. L.: Dissecting Aneurysms of the Aorta, Arch. Int. Med. **84**:558-568 (Oct.) 1949.

33. McGeachy, T. E., and Paullin, J. E.: Dissecting Aneurysm of Aorta, J. A. M. A. **108**:1690-1698 (May 15) 1937.

34. Baer, S., and Goldburgh, H. L.: The Varied Clinical Syndromes Produced by Dissecting Aneurysms, Am. Heart J. **35**:198-211, 1948.

35. Oppenheim, F.: Gibt es eine Spontanruptur der gesunden Aorta und wie kommt sie zustande? München. med. Wchnschr. **65**:1234-1237, 1918.

Simpson,[35] and Mortiz [40] have shown that the normal aorta is capable of withstanding many times the tension resulting from the most extreme elevation of arterial pressure observed in vivo. Furthermore, Robertson and Smith [36] found that to split the planes of the unaltered aortic media, a pressure far in excess of severe hypertension is required. The in vivo experiments of Wartman and Laipply [37] appear to verify the latter observation: They found that the direct injection of blood into the media of arteries of dogs was followed not by dissection but by organization. Such information clearly indicates that factors other than hypertension, specifically those causing foci of medial weakening, are essential to the development of dissecting aneurysm. It would be an error, however, to ignore the association of dissecting aneurysm and elevated arterial tension.

The foregoing observations regarding the nature of the aortic lesions seem to clarify the relation of hypertension and the genesis of hemorrhagic dissection. Degenerative aortic medial lesions, generally of minor extent, are not accompanied by dissecting aneurysm [29] in such a wide variety of conditions that no etiologic inferences seem warranted. These nondissecting lesions are by no means limited to hypertensive individuals. Repair of the weakened foci is rather ineffectual; myxomatous tissue appears, together with vascularization of the affected aortic media. The comparatively slow and bland nature of the reaction leaves the vasa, characteristically thin walled, widely patent, with little support from the surrounding tissue. Rupture of the vasa is considered the primary event in the actual process of dissection. Elevated blood pressure, although not essential, would increase the chances of such intramural vascular rhexis. Inasmuch as hypertension is much less frequently associated with dissecting aneurysm in young individuals, it might be inferred either that degeneration of the elastic tissue variety prevalent in the younger group weakens the aortic media more seriously than does the depletion of smooth muscle more usual in the older group, or that the time factor permits even less reparative change in the young.

RELATION OF INTRAMURAL HEMORRHAGE AND DISSECTING ANEURYSM OF THE AORTA

An intramural hemorrhage occurring in a focus of medial weakening does not invariably lead to dissection. If the fault is isolated, absorption and organization may take place, as Wartman and Laipply [37] have demonstrated experimentally. Absorption of an intramedial hematoma underlying the intima appears to be ineffectual, especially as in a number of instances the hematoma was transformed into an amorphous mass rich in cholesterol. At a late stage, except for the abruptness of the medial defect, such a lesion could not be distinguished from one originating in the intima, an observation which lends support to the views of Winternitz, Thomas, and LeCompte [38] regarding the importance of the vasa vasorum to the genesis of arteriosclerosis. On the other hand, foci of hemorrhage just beneath the adventitia seem to be absorbed and organized more effectively (Fig. 3*B*). The presence of contiguous foci of weakening is essential to the spread of an intramural

36. Robertson, J. S., and Smith, K. V.: An Analysis of Certain Factors Associated with the Production of Experimental Dissection of the Aortic Media, in Relation to the Pathogenesis of Dissecting Aneurysm, J. Path. & Bact. **68**:43-49, 1948.

37. Wartman, W. B., and Laipply, T. C.: The Fate of Blood Injected into the Arterial Wall, Am. J. Path. **25**:383-395, 1949.

38. Winternitz, M. C.; Thomas, R. M., and Le Compte, P. M.: The Biology of Arteriosclerosis, Springfield, Ill., Charles C Thomas, Publisher, 1938.

hemorrhage,[36] and these foci, since they interrupt additional vasa vasorum, lead to secondary ischemic changes favoring progression of the lesion. It is obvious that extension requires extravasation of blood under arterial pressure but, as the reported cases prove, the usual intimal tear is not an essential feature.

SIGNIFICANCE OF CONGENITAL ANOMALIES IN THE GENESIS OF DISSECTING ANEURYSM OF THE AORTA

In the previous discussion no consideration was given to the genesis of the essential medial lesion except as it pertained to ischemia or hypertension. A helpful lead was uncovered in the course of a study of dissecting aortic aneurysms in young individuals, during which an unusual number were observed to be associated with congenital abnormalities. Since morphologic defects may not become manifest until some time after birth, it seemed reasonable to postulate a congenital metabolic defect which also becomes apparent morphologically only after the passage of time and the operation of unknown influences. Such a biochemical lesion explains the localization of the anatomic lesions. The proximal aorta, because of the greater physiologic stress to which it is subject, demands a more active metabolic exchange for the maintenance of its integrity. Any metabolic inadequacy would become manifest first and most prominently in a site of stress, and degenerative medial aortic lesions are most frequent in the proximal aorta. Hypertension would clearly operate to magnify or accelerate such a process. That spontaneous rupture and dissecting aneurysm are also more frequent in the proximal aorta is no doubt attributable to the greater mechanical stress to which this segment is subject. Supporting this conclusion is the observation that the intimal tears associated with dissecting aneurysm are located at the anatomic sites of relative fixation of the mobile aortic arch, namely, the aortic valve ring, the right pulmonary artery, possibly the pericardial reflection, and the insertion of the ligamentum arteriosum arteriae pulmonalis.[8c]

Until the existence of the metabolic defect has been substantiated and its nature defined, the term "idiopathic medial degeneration" seems the most appropriate designation for the process underlying dissecting aneurysm.

SUMMARY

There is general agreement that medial degeneration is essential to the pathogenesis of dissecting aortic aneurysm, even though it does not invariably lead to dissection. Opinion is much less unanimous regarding the initial event which leads to exploitation of the weakness of the aortic wall. Twenty-three cases in which intimal breaks were absent are cited as evidence that the primary hemorrhage is intramural. The microscopic alterations occurring within the aorta in cases of dissecting aneurysm that came to necropsy lend credence to this view and serve to explain it. Associated with the degeneration of the muscular or the elastic laminae of the media is an inadequate reparative reaction characterized by an increase in the number of vasa, a mild inflammatory infiltration, and the appearance of variable quantities of myxomatous tissue. In contrast to the vascular features of syphilitic aortitis, the vasa are thin walled, widely patent, and are supported only by considerably weakened media. The vulnerability of such vessels to rhexis serves to explain, partially at least, the frequency with which hypertension is associated with dissecting aneurysm of the aorta.

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ACCUMULATION OF FAT IN THE LIVER WITH DEFICIENCIES OF THREONINE AND OF LYSINE

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IT SEEMS reasonable to assume that an organ of high metabolic activity and largely protein in structure such as the liver would be affected both as to structure and function if the animal were fed a diet deficient either in protein or in specific amino acids. Bauer and Berg [1] observed that in the mouse a deficiency of threonine resulted in marked edema and ascites, while no similar symptoms were seen with deficiencies of other amino acids. In the growing rat acute lysine deficiency causes hypoproteinemia,[2] which may be associated with reduced blood and plasma volume.[3]

Gillespie and co-workers [4] found no increase of fat in livers of rats fed a lysine-deficient diet in which zein was the protein used. More recently Geiger and Hagerty [5] have shown that a commercial zein preparation, even when supplemented to bring the amino acid level to that of casein, did not promote satisfactory growth of young rats because of a failure of proteolytic enzymes to digest the zein completely. Kligler and Krehl,[6] also obtained better growth with zein diets if the diets were supplemented with arginine, threonine, and valine in addition to lysine and tryptophan, or with 5% of casein. Osborne and Mendel [7] observed that "the growth of rats on a food of zein + lysine + tryptophan has not always been as rapid and prolonged as we might expect." Other investigators have also been unable to

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obtain normal growth on a zein diet supplemented with various amino acids.[8] These observations suggest that when lysine deficiency is produced in rats with zein diets as generally used it is probably complicated by a suboptimal degree of availability of other amino acids.

The relation of methionine to fatty livers is well known.[9] More recently Adamstone and Spector[10] found a heavy accumulation of fat with vacuolation of the cytoplasm of cells in the livers of rats on a tryptophan-deficient diet. The nuclei contained large masses of chromatin and had a single enlarged nucleolus rather than the several nucleoli usually seen. Maun and associates[11] observed that in the livers of rats fed a leucine-deficient diet for 28 days, there was a deposition of fat in a narrow zone about the central veins. No such change was observed in phenylalanine[12] or in histidine deficiencies.[13]

In a study of a number of rats on threonine- and lysine-deficient diets,[14] the observation of a gross fatty appearance of the livers led us to investigate the microscopic tissue changes in the organ which might result from these deficiencies.

EXPERIMENTAL PROCEDURE

Twenty-one Wistar-strain rats from seven litters were fed a threonine-deficient diet ad libitum, and 18 litter mates were pair-fed a control diet. The composition of the control diet is given in Table 1; the age when the rats began to be fed the diet, and the number of days they were fed the diet are shown in Table 2. The amino acid mixture is similar to that used by Maun and associates[12] and supplied approximately three times the minimum requirement of each of the essential amino acids. In the deficient diet the threonine was replaced by sucrose.

To study the effects of lysine deficiency, 10 rats from three litters were fed a lysine-deficient diet ad libitum while 9 litter mates were pair-fed the control diet shown in Table 1. The lysine-deficient diet was similar to the control diet except that the lysine was replaced with sucrose. The rats were given the diet when 27 or 28 days of age and were fed the diet for 48 or 63 days.

Threonine-deficient rats and controls 1308 to 1322, inclusive, were killed by exsanguination under urethan-pentobarbital anesthesia. The remaining rats were killed by crushing the necks. A piece of the left half of the median lobe of each liver was immediately fixed in 1:10 formalin. Sections were examined microscopically after the use of a routine hematoxylin-eosin stain. In addition, frozen sections of each liver were examined after staining with Sudan IV by Herxheimer's method. Osmium tetroxide was also used in a few instances. Liver fat was determined as described by Tucker and Ekstein.[9]

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TABLE 1.—*Composition of Diets Used*[*]

	Control Diet[†] Gm.		Mg.
l-Lysine monohydrochloride	4.0	Riboflavin	1.6
dl-Tryptophan	0.8	Thiamine hydrochloride	0.4
l-Leucine	2.6	Calcium pantothenate	2.0
dl-Isoleucine	3.2	Pyridoxine hydrochloride	0.4
dl-Valine	4.5	Niacin	2.0
dl-Methionine	1.9	Biotin	0.02
l-Arginine hydrochloride	0.8	Folic acid	0.2
l-Histidine hydrochloride	1.6	Inositol	20.0
dl-Phenylalanine	2.2	p-Aminobenzoic acid	10.0
dl-Threonine	3.2		
Sucrose	66.0		
Salt mixture[‡]	4.0		
Cod liver oil	2.0		
Cottonseed oil	3.0		
Choline hydrochloride	0.3		

[*] The threonine-deficient and lysine-deficient diets were similar to the control diet except that the particular amino acid in the formula was replaced by an equal amount of sucrose.

[†] The control diet was supplemented by administering once a week a solution of menadione U. S. P. (2-methyl-1,4-naphthoquinone) and alpha-tocopherol in cottonseed oil so that each rat received an average of 1 mg. of the former and 0.07 mg. of the latter per day.

[‡] The salt mixture was that used by J. M. McKibben, R. J. Madden, S. Black, and C. A. Elvehjem (Am. J. Physiol. 128:102, 1939).

TABLE 2.—*Experimental Results on Threonine-Deficient Rats and Pair-Fed Control Rats*

Type of Diet and Age Started, Days	Rat	Days on Diet	Food Intake per Day, Gm.	Change in Weight	Liver Weight	Liver Fat, %	Gross Appearance	Fatty Changes at Microscopic Examination
Deficient (28)	1368	36	2.2	−14.8	....	6.27	.....	Pronounced
Control	1370	36	2.2	−10.9	....	4.80	.....	No fat visible
Deficient (28)	1310	36	2.0	−18.1	....	7.77	.....	Pronounced
Control	1311	36	2.0	− 1.7	....	4.39	.....	No fat visible
Deficient (28)	1312*	34	1.8	−14.5	....	....	.....	.....
Control	1313	34	1.8	−10.4	....	4.33	.....	No fat visible
Deficient (28)	1314*	25	2.2	−15.2	....	....	.....	.....
Control	1315	33	2.2	− 7.0	....	....	.....	.....
Deficient (28)	1316	34	1.7	−10.4	....	4.80	.....	Slight
Control	1317*	29	1.7	− 8.5	....	....	.....	Slight
Deficient (28)	1318	35	2.5	−12.6	....	7.83	.....	Pronounced
Control	1319	35	2.5	−10.4	....	5.91	.....	Slight
Deficient (28)	1320	35	3.4	−18.1	....	5.95	.....	Pronounced
Control	1321	35	3.4	− 6.2	....	4.39	.....	No fat visible
Deficient (28)	1322	35	3.0	−22.4	....	4.77	.....	Slight
Deficient (66)	1354	69	4.4	−33.7	....	9.51	Pale yellow	Pronounced
Control	1355	69	4.4	+21.4	....	4.91	Red-brown	Insignificant
Deficient (66)	1356*	59	3.7	−38.6	....	....	.....	.....
Control	1357	59	3.7	−16.9	....	....	.....	.....
Deficient (36)	1364	56	2.5	−23.2	3.37	20.10	Pale yellow	Pronounced
Control	1365	56	2.6	−24.0	2.17	3.14	Red-brown	No fat visible
Deficient (36)	1366	56	3.1	−30.9	4.25	12.51	Pale yellow	Pronounced
Control	1367	56	3.2	−14.5	1.99	2.68	Red-brown	No fat visible
Deficient (36)	1368	56	2.7	−29.8	3.80	24.08	Pale yellow	Pronounced
Control	1369	56	2.8	−12.2	1.75	3.59	Red-brown	No fat visible
Deficient (36)	1370*	55	5.3	− 9.0	....	....	.....	.....
Deficient (56)	1396	79	2.7	−46.0	3.75	6.17	Moderately yellow	Pronounced
Control	1397	79	2.7	− 9.5	2.35	5.02	Dark red	No fat visible
Deficient (56)	1398	79	3.3	−48.7	5.65	7.96	Pronounced yellow	Pronounced
Control	1399	79	3.3	−13.4	3.54	2.82	Red-brown	No fat visible
Deficient (56)	1400	79	3.7	−35.1	3.55	7.43	Moderately yellow	Moderate
Control	1401	79	3.7	+ 3.4	3.09	5.15	Dark red	Insignificant
Deficient (56)	1402	79	2.9	−37.0	3.07	8.06	Pronounced yellow	Moderate
Deficient (56)	1403	79	5.4	−42.9	3.60	7.23	Pale; yellowish	Moderate
Control	1404	79	5.4	+30.8	4.31	5.33	Dark red	Insignificant
Deficient (56)	1405	79	3.2	−43.7	4.08	4.98	Pale; yellowish	Slight
Control	1406	79	3.2	−11.3	2.33	4.92	Dark red	No fat visible
Deficient (56)	1407	79	7.9	−39.4	3.50	6.87	Moderately yellow	Moderate
Control	1408	79	7.9	+48.6	5.15	5.53	Red-brown	Insignificant

[*] Rat died.

RESULTS

As may be seen in the results reported in Table 2, a significant accumulation of fat was observed in the liver of each of the 17 threonine-deficient rats which lived to the conclusion of the experiment and in 2 of the 16 control rats.

In these animals vacuoles were found in the cytoplasm of the hepatic cells after hematoxylin-eosin staining, but the glycogen present in the cytoplasm made direct appraisal difficult. With the use of Sudan IV and osmium tetroxide stains, it was easy to ascertain the size of vacuoles or fat droplets and the extent of involvement of each lobule. The fat droplets, which were of small and medium size, distended the cytoplasm of the involved hepatic cells. In the liver of rats with the most extensive fatty change, these swollen cells compressed the sinusoids. The nuclei were usually centrally placed in the cells, and in no instance did we find the type of fat droplet which usually displaces the nucleus to one side. The nuclei of the hepatic cells were larger than normal and otherwise altered in the liver of rats with the greatest fat accumulation. The nuclear chromatin was somewhat clumped and widely dispersed, the nucleoli were unduly prominent, and there tended to be one large nucleolus instead of the usual two to four smaller nucleoli. These nuclear changes were similar to those noted by Adamstone and Spector [10] in experimental tryptophan deficiency. The nuclear membrane was well defined and without thickening. The nuclei of the hepatic cells of the control rats appeared to be normal.

The degree of involvement of the liver was divided into three categories: (1) minimal or slight changes when fat droplets were seen only in a narrow zone of the hepatic lobule, around the central vein; (2) moderate changes when fat droplets were present in both the central and the midzone area, and (3) pronounced or extensive involvement if droplets were seen throughout almost the entire lobule. In many instances the periportal areas were spared in the latter group. The accumulation of fat was extensive in the livers of 10 of the 17 threonine-deficient rats, moderate in those of 4, and slight in those of 3. Two of the 16 control rats had a slight accumulation of liver fat; in 4 there was an insignificant amount of fat, which consisted of a few scattered fat globules, while in the remaining 10 rats no fat droplets were visible in the sections. No nuclear changes were observed in the hepatic cells of the control rats.

In the livers of the lysine-deficient rats the fatty changes of the cytoplasm and the nuclear changes observed were similar to those seen in the threonine-deficient rats, although these changes developed most slowly. The nuclear changes were less prominent than in the threonine-deficient rats. In a smaller proportion of the hepatic cells there was a single large nucleolus rather than several smaller nucleoli. No nuclear changes were observed in the hepatic cells of the control rats. Of 10 lysine-deficient rats (Table 3), 3 showed pronounced accumulation of liver fat, 4 a moderate accumulation, 1 a slight, and 1 an insignificant amount of fat. Two of nine control rats showed a few scattered fat droplets, while in the remaining seven no fat droplets were visible in the liver sections.

In general the percentages of fat in the livers of the threonine- and lysine-deficient rats were higher than those in the control livers, although in some instances the difference in level was not striking. As may be seen from the liver weights, the livers of the deficient rats were usually larger than those of the control rats, although generally the deficient rats suffered a greater loss in body weight than did their

pair-fed controls. The considerable growth of Control Rats 1355, 1404, 1408, and 1337 during the course of the experiment was probably due to a higher food consumption resulting from the scattering of food by the paired deficient rats. The difference between the results obtained in this study and those obtained by Gillespie and co-workers [4] can probably be attributed to the differences in diets used, in age of the animals and other experimental conditions.

The fact that an accumulation of liver fat and certain nuclear changes were found in both threonine and lysine deficiency of the rat and that Adamstone and Spector [10] found similar changes in tryptophan deficiency leads to the suggestion that these changes are not a specific effect of a particular deficiency but rather the effect of a failure of certain cell functions resulting from reduced protein anabolism. This view finds support in the work of Miller,[15] who recently has shown that rats

TABLE 3.—*Experimental Results on Lysine-Deficient Rats and Pair-Fed Control Rats*

Type of Diet	Rat	Days on Diet	Food Intake per Day, Gm.	Change in Weight	Liver Weight	Liver Fat, %	Gross Appearance	Fatty Changes at Microscopic Examination
Deficient	1338	63	3.1	−19.9	3.52	....	Light yellow	Moderate
Control	1339	63	3.1	+69.2	2.54	....	Dark red	No fat visible
Deficient	1340	63	2.8	−18.4	2.60	....	Light yellow	Moderate
Control	1341	63	2.8	− 5.0	2.57	....	Dark red	No fat visible
Deficient	1342	63	3.8	−21.2	2.95	....	Pale red	Slight
Control	1343	63	3.8	+15.1	2.55	....	Dark red	No fat visible
Deficient	1344	63	2.7	−18.3	2.31	....	Pale red	Insignificant
Deficient	1428	48	2.3	−16.4	2.80	9.50	Pale yellow	Pronounced
Control	1429	48	2.3	−14.3	2.16	2.10	Dark red	Insignificant
Deficient	1430	48	2.7	−16.6	2.76	2.87	Moderately yellowish	Pronounced
Control	1431	48	2.7	− 4.1	2.24	2.76	Dark red	Insignificant
Deficient	1432	48	2.5	−14.0	2.61	2.37	Pale yellowish	Slight
Control	1433	48	2.5	− 0.5	2.31	1.48	Dark red	No fat visible
Deficient	1434	48	2.6	−11.8	2.93	3.51	Moderately yellowish	Moderate
Control	1435	48	2.6	+ 0.8	2.80	0.91	Dark red	No fat visible
Deficient	1436	48	2.1	−12.3	2.27	2.44	Slightly yellowish	Moderate
Control	1437	48	2.1	− 4.9	2.01	1.65	Pale red	No fat visible
Deficient	1438	48	2.2	− 7.3	2.38	....	Pale yellow	Pronounced
Control	1439	48	2.2	+ 0.6	1.89	....	Pale red	No fat visible

restricted to low-protein or nonprotein diets showed a nonspecific loss of activity of the five liver enzymes for which he tested, along with the loss of liver protein.

According to Muntwyler and associates,[16] dietary protein restriction results in a reduction of the protein in all of the morphological components of the liver, including the mitochondria. Enzymes concerned in lipid metabolism in the liver are localized in the mitochondria.[17]

Other investigators have found that a diet low or lacking in protein resulted in a reduction of liver enzyme activity.[18] A similar reduction of liver enzyme activity has been noted in methionine deficiency.[19] It is to be expected that a similar nonspecific reduction of liver enzyme activity might occur in deficiencies of any of the

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essential amino acids. It seems reasonable to suppose that in threonine and lysine deficiencies there may be a reduction of the amount of the enzymes which are concerned in fat metabolism and fat turnover, with the result that fat accumulates in the hepatic cells.

Dunn and co-workers [20] studied the renal excretion of amino acids in cases of human liver disease and found that in the majority of the cases the values obtained for urinary threonine were normal while almost half of the lysine values were low. This probably may be considered further evidence implicating lysine as an amino acid of importance in normal liver function.

In small groups of rats fed diets similar to those described above and containing adequate amounts of choline but devoid of phenylalanine, methionine, or protein, no marked accumulation of fat was seen such as was observed to occur in threonine and lysine deficiencies.

SUMMARY

In rats it was found that feeding a threonine-deficient diet resulted in enlarged and grossly fatty livers. On microscopic examination it was found that small and medium-sized fat droplets distended the cytoplasm of the hepatic cells around the central vein. In 10 of 17 rats the fatty changes extended to or nearly to the periphery of the lobule. Determinations of liver fat showed higher values for the deficient rats than for the control rats. The nuclear chromatin of the hepatic cells of the threonine-deficient rats was clumped and widely scattered, and there tended to be one prominent nucleolus instead of several nucleoli.

The changes observed in the livers of the lysine-deficient rats were less marked although similar in character.

Dr. Edgar R. Pund gave advice and assistance. Dr. A. B. Chandler checked some of the tissue sections for the authors.. Miss Josephine Hatch prepared the tissue sections. Sheldon Cohen and Edgar McDaniel cared for the animals, and Henry Scoggins supplied technical assistance. This investigation was supported by a research grant from the National Institute of Health, United States Public Health service. A part of the amino acids used was donated by Winthrop-Stearns, Inc., New York.

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OVARIAN STROMAL HYPERPLASIA IN BREAST CANCER

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THE FREQUENT association of diseases of the uterus and the breast is generally ascribed to the fact that both organs participate in the processes of reproduction, with the attendant hormonal stimuli and opportunities for pathologic imbalance.

As part of an investigation of various endocrine alterations accompanying cancer, ovaries were examined morphologically for stigmata of hormonal imbalance. Since the work of G. V. S. Smith,[1] ovarian cortical stromal hyperplasia has been emphasized as a frequent accompaniment of endometrial carcinoma. Smith observed abnormally abundant whorled masses of stromal cells in ovaries in 87% of 180 endometrial carcinomas. Later Woll, Hertig, Smith, and Johnson [2] reported cortical stromal hyperplasia in ovaries from 84% of 331 endometrial cancer patients, in contrast to an incidence of 44% in a control series.

PRESENT STUDY

A series of 100 cases of breast cancer in which autopsies were performed was obtained from the files of the Pondville Hospital (Massachusetts Department of Public Health) and the New England Deaconess Hospital. No attempt at selection was made, and the cases were not necessarily consecutive. Most autopsies examined included available routine ovarian sections. Some cases were excluded because of lack of microscopic preparations, inadequacy of available sections, or because of extensive metastatic tumor replacing ovarian tissue. Cases of hormonally treated inoperable breast cancer were also excluded. Only one patient had received x-radiation to the ovaries (600 r). A control group of 133 patients of comparable ages with no demonstrable malignant neoplasms at autopsy was obtained from the same files.

From the Departments of Pathology of the Pondville Hospital, Commonwealth of Massachusetts, P. O. Walpole, Mass., and the New England Deaconess Hospital, Boston.

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MORPHOLOGIC CRITERIA

In general the observations of Woll and associates [2] served as criteria. The ovarian cortex was found to be increased in thickness and cellular density in cortical stromal hyperplasia, sometimes forming spherical scalloped masses with small papillary excrescences projecting from the surface. A corrugated appearance of the cut section was common. Microscopically, the stromal cells were disposed in numerous whorls or interlacing fascicles, which wove about variable numbers of capillaries (Fig. 1*A*). The nuclei of cortical stromal cells were enlarged, blunted, with abundant coarse granular chromatin. There was minimal deposition of intervening stroma or collagen, giving an appearance of great cellularity (Fig. 1*B*). Hyperplastic stromal masses dipped irregularly into the relatively acellular, eosinophilic medullary stroma, in contrast to the thin cortex of atrophic ovaries (Fig. 2*A*).

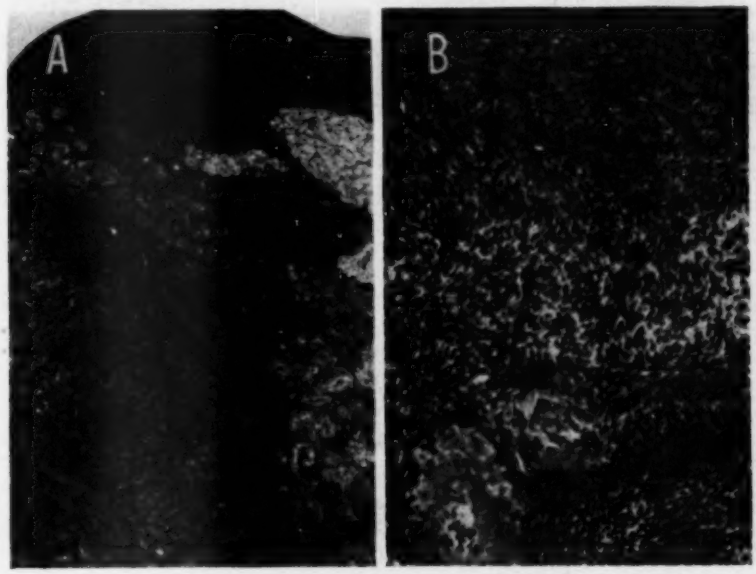

Fig. 1.—*A*, section of ovarian cortex demonstrating stromal hyperplasia as dark-staining cellular tissue. Hematoxylin and eosin; × 21.

B, detail of hyperplastic cortical stroma with interlacing cell fascicles and clear areas which contain lipid. Hematoxylin and eosin; × 125.

Among the more striking examples of cortical stromal hyperplasia additional changes were observed. Small, poorly demarcated clear spaces in the ground substance were exaggerated in size and number. In such instances fat stains usually indicated increased amounts of lipid. Small nodular areas were observed composed of frankly lipid-laden cells with round hyperchromatic nuclei and prominent nucleoli. Well-demarcated cell margins and clear intercellular zones were present (Fig. 2*B*). The term "thecomatosis" hereto applied by Woll and associates [2] refers to the interpretation that these masses represent luteinized thecal stromal cells. Such foci at times attracted lymphocytes or macrophages to form small leucocytic

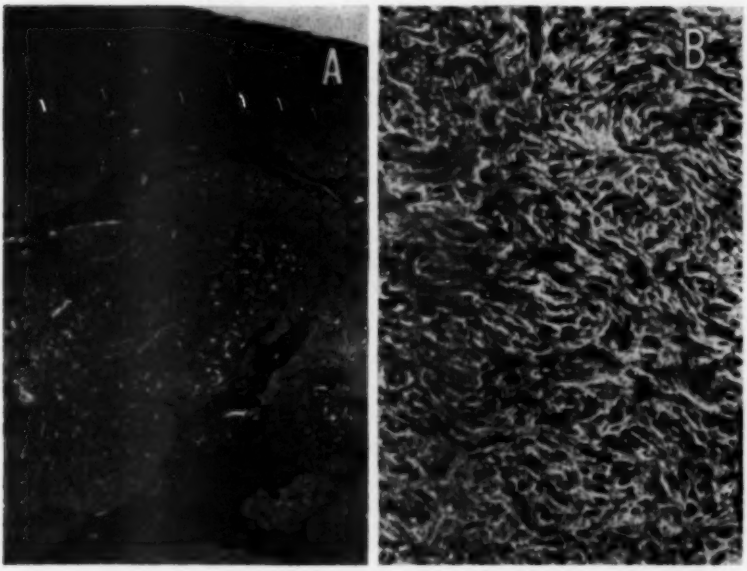

Fig. 2.—*A*, atrophic postmenopausal ovary. A normally thin layer of superficial stroma is present, in contrast to Figure 1*A*. Hematoxylin and eosin; × 21.

B, thecomatosis of ovarian cortical stroma. It is recognized by a coarse interlacing pattern with intercellular spaces, shown by special stains to contain fat. Hematoxylin and eosin; × 300.

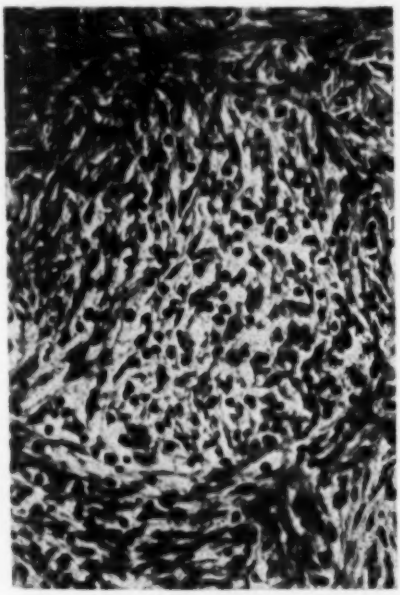

Fig. 3.—Cortical granuloma of ovarian cortex, consisting of a leucocytic infiltration of lipid-rich stroma. Hematoxylin and eosin; × 300.

masses called cortical granulomas (Fig. 3). These are thought to arise from lipoid leucotaxis.

Sometimes an alteration of medullary stroma was also observed, consisting of increased tortuosity and perhaps increased number of blood vessels in the ovarian hilus. Numerous thick-walled small vessels, largely arterioles, formed an angiomatoid plexus of quite bizarre and characteristic appearance. In the absence of information that this change has been previously described, it has been termed medullary vascular hyperplasia (Fig. 4*A*). Its origin is unexplained, but it is suspected to be a local manifestation of excess estrogenic growth stimulation on vascular tissue. This type of vascular stimulation is well known elsewhere, as in the endometrium [3] and the skin.[4]

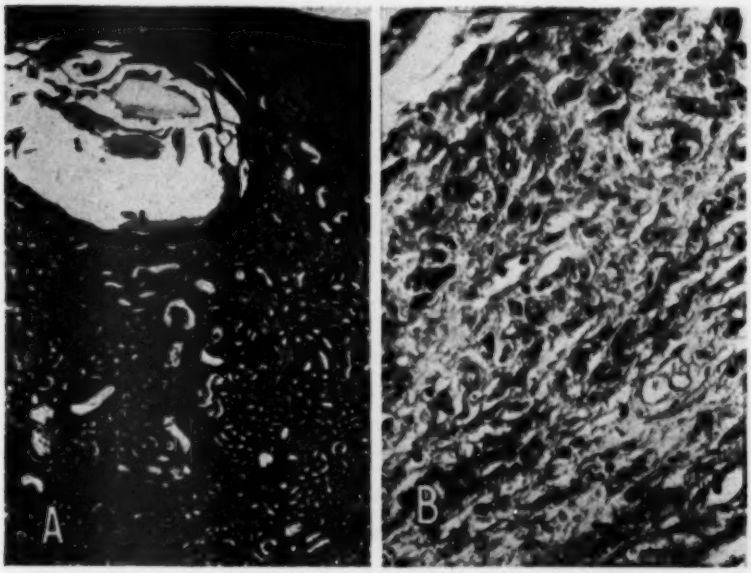

Fig. 4.—*A*, medullary vascular hyperplasia of ovary, with close-packed angiomatoid vascular plexi. The large space is a follicular cyst. Hematoxylin and eosin; × 21.

B, portion of ovarian hilus, with increased hilar cells, resembling interstitial cells of testis. A capsule-shaped Reinke crystalloid is shown. Hematoxylin and eosin; × 300.

The ovarian hilar cells, which resemble adrenal cortical cells,[5] were sought and frequently found in both breast cancer and control series. No morphologic or quantitative abnormalities were observed in either group, except for one instance of hilar cell hyperplasia in the cancer group (Fig. 4*B*).

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RESULTS

As indicated in Table 1, cancer of the breast was found to be accompanied by ovarian stromal hyperplasia in 83 of 100 cases, with the same relatively high incidence among all age groups examined. In contrast, the control series (Table 2) showed this change in 50 of 133 cases (37.6%), which is comparable to previous reports.[2] The slightly lower control incidence may perhaps be attributed to the fact that a larger number of relatively younger patients were included in our control

TABLE 1.—*Cases of Carcinoma of the Breast: Incidence of Ovarian Stromal Hyperplasia*

Age group	Cases	Cortical Stromal Hyperplasia	Medullary Vascular Hyperplasia	Absence of These Changes	% Cortical Stromal Hyperplasia
30-39	5	4	..	1	80.0
40-49	22	18	2	4	81.8
50-59	26	21	3	5	80.7
60-69	25	22	5	3	88.0
70-79	17	14	1	3	82.3
80-89	5	4	..	1	80.0
Total	100	83	11	17	83.0

TABLE 2.—*Non-Neoplastic Controls: Incidence of Ovarian Stromal Hyperplasia*

Age Group	Cases	Cortical Stromal Hyperplasia	Absence of This Change	% Cortical Stromal Hyperplasia
30-39	22	9	13	40.9
40-49	32	7	25	21.8
50-59	34	17	17	50.0
60-69	23	11	12	47.8
70-79	17	4	13	23.5
80-89	5	2	3	40.0
Total	133	50	83	37.5

TABLE 3.—*Incidence of Ovarian Stromal Hyperplasia in Different Types of Breast Cancer*

Type	Cases	Cortical Stromal Hyperplasia	Absence of This Change
Carcinoma simplex	85	70	15
Adenocarcinoma	9	7	2
Papillary adenocarcinoma	3	3	0
Paget's disease, carcinoma simplex	1	1	0
Fibrosarcoma	2	2	0

series. The relation between the pathologic types of breast cancer and stromal hyperplasia is shown in Table 3.

In addition to the strikingly higher incidence of ovarian stromal hyperplasia with breast cancer, the increased degree of hyperplasia was notable. Changes were generally relatively mild among the ovaries of the control series, and only one instance each of theconatosis and cortical granuloma formation was encountered. In contrast, among the breast cancer cases there were 18 with thecomatosis and 10 with cortical granulomas. The one case of hilar cell hyperplasia has been mentioned.

Medullary vascular hyperplasia accompanied cortical hyperplasia in 11 cancer cases and in 2 of the control group.

COMMENT

Since there is general acceptance of the important role of estrogenic hormones in breast physiology and pathology, the unusual frequency of ovarian changes thought to indicate antecedent excess estrogenic secretion accompanying breast cancer is not unexpected. The present study provides morphologic evidence for this in human material.

Ovarian stromal hyperplasia has as yet not been investigated with hormonal assay procedures, and judgment of its significance is based on the estrogen production inferred from its lipid-rich cells. The importance of this change in evaluating carcinogenic stimuli to endometrium and breast lies in the relative permanence of ovarian stromal changes. End-organ responses to estrogens produced have ample opportunity to develop and subside as carcinoma is established and pursues its natural course at the expense of functioning tissues. Thus morphologic alterations of vaginal epithelium and endometrium attributable to estrogens cannot be expected in women dead of breast cancer. However, ovarian cortical stromal overgrowth remains as evidence that estrogen production was increased in the past. The presence of medullary vascular hyperplasia suggests an effect of abnormal or prolonged estrogenic stimulation.

That ovarian stromal hyperplasia might be a by-product of carcinoma growth with its associated tissue damage is not disproved. But it does not accompany frequently a variety of other cancers investigated in women, with a few exceptions to be analyzed in a future study.

Various abnormalities of endocrine balance have been described in the presence of carcinoma of the breast.[6] Thus, about three-fourths of normal women pass through the menopause during the fifth decade, while about one-half of those with cancer of the breast are still menstruating at the age of 50.[7] Likewise, about five times as many women with breast cancer have a late menopause as normal women. The rapidity of growth and the grave prognosis of a carcinoma of the breast occurring coincidentally with pregnancy are well known and need no comment. Breast tumors occurring during the period of sexual activity grow more rapidly and are more highly malignant than those occurring after the period of the menopause.

Evidence derived from animal experimentation is much more accurately defined and clearly delineated, indicating three separate and distinct etiologic factors, i. e., (1) heredity, (2) ovarian hormonal stimulation, and (3) the milk factor of Bittner. Thus, in highly susceptible strains of mice (*a*) castration was followed by a definite decrease in the incidence of spontaneous mammary carcinoma[8]; (*b*) Murray[9] noted that mammary cancer was produced in males by transplantation of ovarian

6. Nathanson, I. T.: Hormones in Relation to Tumors of the Female, in Meigs, J. V., and Sturgis, S. H.: Progress in Gynecology, New York, Grune & Stratton, Inc., 1950, Vol. 2.

7. Olch, I. Y.: Menopausal Age in Women with Cancer of Breast, Am. J. Cancer **30**:563-566, 1937.

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tissue, and (*c*) Lacassagne [10] was able to produce cancer in males by the administration of estrogen.

The basis of these ovarian changes is not settled. Comparable ovarian cortical stromal activity can be produced, however, by anterior pituitary hyperfunction [11] or by follicle-stimulating and luteinizing gonadotropins.[12] Both in endometrial and breast carcinoma circumstantial indications direct suspicion at antecedent malfunction of the anterior lobe of the pituitary gland, operative through the ovary and perhaps directly as well.

SUMMARY

Ovaries of 83 of 100 women with breast cancer examined after death showed morphologic evidence of cortical stromal hyperplasia. The incidence of this finding in a control series was 37.6%. Eleven of the cancer patients also had ovarian medullary vascular hyperplasia. One patient showed abnormally increased ovarian hilar cells. In the breast cancer series, ovarian stromal hyperplasia was more outstanding, with relatively more frequent thecomatosis and cortical granuloma formation. The alterations described are considered morphologic stigmata of hyperestrinism, most likely secondary to overstimulation of the anterior lobe of the pituitary. Together with extant clinical and experimental knowledge the findings presented emphasize endocrine factors in the etiology of breast cancer.

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MYCOSIS OF CERVICAL SPINAL CORD FOLLOWING INTRATHECAL PENICILLIN THERAPY

Report of a Case Simulating Cord Tumor

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MYCOTIC infections occurring in individuals treated with penicillin and other antibiotics have been recently reported.[1] Evidence of experimental enhancement of the growth of certain fungi by antibiotic agents has also appeared in the literature.[2] Fatalities may even occur from mycotic infections during therapy with these drugs. This problem has become so important that the Council on Pharmacy and Chemistry of the American Medical Association has advocated that a warning statement be included in the labeling of aureomycin and other antibiotic drugs to the effect that fungi may flourish in tissues and lesions when the normal or the abnormal bacterial flora is suppressed.[3]

The following case is presented as an unusual instance of mycotic granuloma that involved the cervical spinal cord and clinically simulated a spinal cord neoplasm. It is believed that this is the first reported case of mycotic infection of the meninges associated with or following the intrathecal administration of penicillin.

CLINICAL FINDINGS

M. D. (U. H. No. 482264), a white housewife, 40, was admitted to University Hospital on March 17, 1948. Her illness had begun three days before with headache and fever. The following day she suffered pain in her neck, became restless, and noted a purulent discharge

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1. (*a*) Zimmerman, L. E.: Candida and Aspergillus Endocarditis with Comments on the Role of Antibiotics in Dissemination of Fungus Disease, Arch. Path. **50**:591-605 (Nov.) 1950. (*b*) Hewitt, W. L., and Williams Jr., B.: Chloromycetin (Chloramphenicol) in the Treatment of Infections, New England J. Med. **242**:119-127, 1950. (*c*) Mangiaracine, A.: Oral Moniliasis Following Antibiotic Therapy, Correspondence, ibid. **244**:655, 1951. (*d*) Woods, J. W.; Manning Jr., I. H., and Patterson, C. N.: Monilial Infections Complicating the Therapeutic Use of Antibiotics, J. A. M. A. **145**:207-211 (Jan. 27) 1951. (*e*) Harris, H. J.: Aureomycin and Chloramphenicol in Brucellosis, with Special Reference to Side Effects, ibid. **142**:161-165 (Jan. 21) 1950. (*f*) Cawley, E. P.: Aspergillosis and the Aspergilli, Arch. Int. Med. **80**:423-434 (Oct.) 1947.

2. (*a*) Campbell, C. C., and Saslaw, S.: Enhancement of Growth of Certain Fungi by Streptomycin, Proc. Soc. Exper. Biol. & Med. **70**:562-563, 1949. (*b*) Foley, G. E., and Winter Jr., W. D.: Increased Mortality Following Penicillin Therapy of Chick Embryos Infected with Candida Albicans var. Stellatoidea, J. Infect. Dis. **85**:268-274, 1949. Woods and others.[1d]

3. Council on Pharmacy and Chemistry: Warning Statement to Be Included in Aureomycin Hydrochloride, Chloramphenicol and Terramycin Hydrochloride Labeling, J. A. M. A. **145**:1267 (April 21) 1951.

from her left ear. The day before admission she became semicomatose and delirious, had severe headache, pain in the neck, and vomited several times. Her past medical history was not remarkable.

On admission she was disoriented and restless. Her skin was hot and dehydrated. The oral temperature was 104 F.; the pulse rate, 144 per minute, and the respirations, 36 per minute. The Kernig and Brudzinski signs were positive bilaterally. The deep tendon reflexes were all 4+, but there was no ankle clonus, and the Babinski toe sign was not present. The cranial nerves showed no functional abnormalities.

The right tympanic membrane was retracted, dusky red, and had a diminished light reflex. Although dried blood was seen in the auditory canal, the tympanum was apparently intact.

Laboratory Data.—On admission the erythrocyte count was 4,600,000, with a hemoglobin content of 12.8 gm. The leucocyte count was 11,200 (neutrophils 90%, lymphocytes 10%).

The admission urinalysis showed 50 mg. of albumin per 100 cc.; there were many hyaline casts, 1 to 3 white blood cells, and 5 to 10 red blood cells per high power field. During the last two weeks of hospitalization urine specimens contained innumerable white blood cells; Proteus vulgaris was cultured from the urine on two occasions.

The initial lumbar puncture showed a pressure of 330 mm. of fluid, with normal dynamics. The spinal fluid was cloudy and contained 4,450 leucocytes per cubic millimeter (neutrophils 77%, lymphocytes 23%). The test for globulin was positive; total proteins amounted to 480.0 mg., sugar to 78.5 mg., and chlorides to 640.2 mg. per 100 cc. Pneumococcus Type III was cultured from the spinal fluid. The growth of the pneumococci was inhibited by 0.02 unit of penicillin per cubic centimeter.

A roentgenogram of the chest showed essentially normal lung fields and a normal cardiac silhouette. The outline of the right frontal sinus was hazy, but the mastoids showed no evidence of infection.

Therapy.—The patient was treated with intramuscular injections of crystalline penicillin and penicillin G procaine (duracillin®), with a total of 6,650,000 units being given over a 16-day period. Intrathecally penicillin totaling 160,000 units was given in doses of 10,000 units, injected twice daily during the critical phase of the disease and then once a day until the 12th hospital day. The spinal fluid penicillin level was maintained between 4 and 8 units per cubic centimeter. A total of 6.3 gm. of sulfadiazine was given and the free sulfonamide blood level maintained between 14 and 16 mg. per 100 cc. One intravenous injection of antipneumococcal rabbit serum was administered on the fifth hospital day. A sulfonamide preparation (sulfadiazine, sulfamerazine, and sulfathiazole; combisul®) and calcium mandelate were given for the urinary tract infection.

Hospital Course.—On the second hospital day, right internal strabismus appeared, but cleared completely in a few days. On the same day there was onset of urinary retention with overflow incontinence, and during treatment of the retention, cystitis developed.

Despite these complications the hospital course was eminently satisfactory. The patient became rational in two days, the fever gradually disappeared, and the spinal fluid findings returned to normal. Twenty days after admission she was discharged, apparently well except for residual weakness in her legs and continuing cystitis, which was to be treated at home.

Subsequent Course.—After she was discharged, vague symptoms of weakness and nervousness gradually developed, associated with tremors of the hands and attacks of dyspnea. Her appetite became poor, and she had episodes of nausea and vomiting. She complained of pain in the shoulders and had difficulty in walking, for which she required a cane.

On Feb. 26, 1951, almost three years after the onset of her pneumococcal meningitis, she was admitted to another hospital, complaining of inability to use her arms and legs. This symptom had been present for the previous three months, and during the preceding nine months she had lost about 30 lb. (13.5 kg.) in weight. Examination revealed an emaciated patient with a large decubital ulcer over the sacrum. There was complete quadriplegia, with a sensory level at the fourth cervical dermatome. The breathing was entirely phrenic, shallow, and very fast, with a rate of 52 respirations per minute. The knee jerks were 2+ on the right and 3+ on the left. Ankle clonus was present on the left and a Babinski toe sign on the right. A lumbar punc-

ture showed a pressure of 35 mm. of spinal fluid, and only a few drops of fluid were obtained. The fluid was bloody and contained 570 mg. of protein per 100 cc. A myelogram was unsatisfactory, but it showed an irregular subarachnoid pattern, and the dye did not rise above the fifth thoracic vertebra.

On the basis of these findings, the neurosurgeon made a diagnosis of cord tumor with arachnoiditis. An upper-thoracic exploratory laminectomy was attempted, but the patient's condition deteriorated before the cord was exposed, and the operation was discontinued. The patient died of respiratory paralysis four hours after the operation.

AUTOPSY

The body was that of an embalmed emaciated white female. It weighed an estimated 75 lb. (34 kg.) and measured 166 cm. in length. There was marked muscular wasting of the extremities, with a wrist drop type of deformity on the right. A recent surgical incision was present over the upper thoracic part of the spinal column and a decubital ulceration 5 cm. in diameter over the sacrum. The

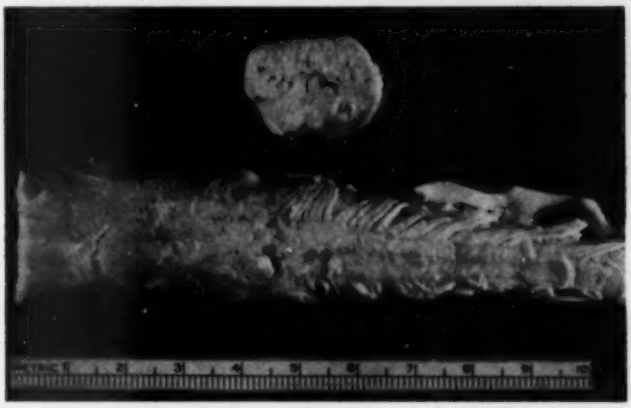

Fig. 1.—Mycotic granuloma of the cervical spinal cord. Above is a cross section of the lesion showing the granulomatous tissue surrounding and distorting the cord. Below is an external view of the ventral surface of the cord. The fusiform swelling produced by the granuloma is seen at the left.

parietal pleura showed ecchymoses along the vertebral column. The urinary bladder was contracted and contained a few small calculi. The mucosa was thickened, hemorrhagic, and covered by a purulent exudate. The remaining thoracic and abdominal organs were essentially normal.

The brain weighed 1,380 gm. The dura was normal. The leptomeninges were thin and transparent. Sections through the cerebral and cerebellar hemispheres, as well as through the brain stem, were grossly normal.

Beginning abruptly at the foramen magnum and extending caudad for a distance of 9 cm. there was a fusiform enlargement of the cervical cord. The swelling was 2.5 cm. in diameter, firm, and adherent to the overlying dura. Cross sections showed a gray-yellow, whorled fibrous tissue averaging 1 cm. in thickness completely encircling the cervical cord (Fig. 1). Although the cord was distorted and compressed by the tissue, it was not grossly invaded. Below the lesion the cord was essentially normal, but the spinal fluid was xanthochromic.

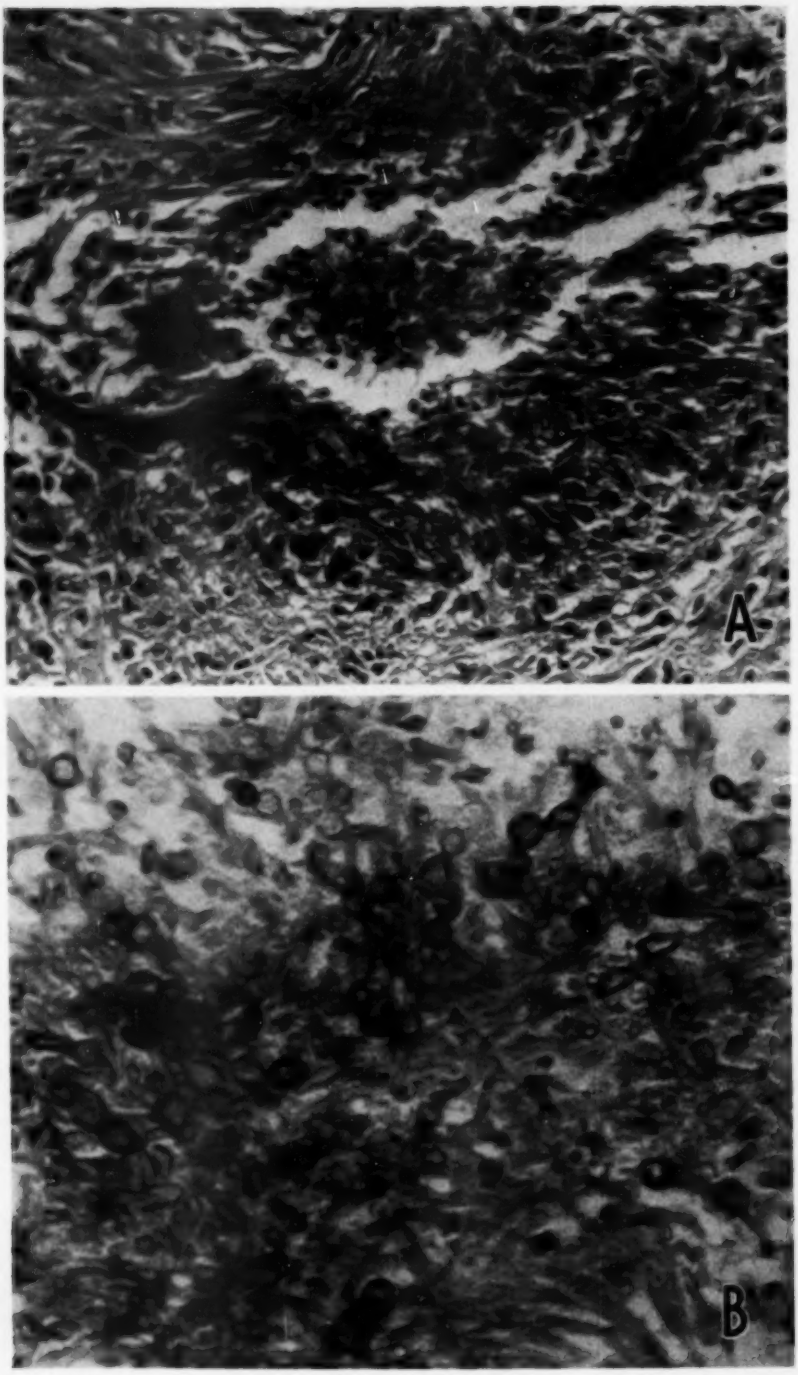

Fig. 2.—*A*, small pseudotubercle of the mycotic granuloma. It is composed of a central collection of hyphae, spores, and cellular debris, surrounded by several multinucleated giant cells, and a peripheral zone of epithelioid cells. Hematoxylin and eosin stain; × 250.

B, hyphae of aspergillus from the center of a pseudotubercle. The hyphae are branching, septate, and contain terminal spores. Hotchkiss-McManus stain; × 625.

MICROSCOPIC OBSERVATIONS

Sections of the lesion surrounding the spinal cord showed chronic inflammatory tissue. The histologic appearance was that of a pseudotuberculous granuloma, with a central collection of neutrophils and necrotic debris surrounded by a zone of epithelioid cells, macrophages, and foreign body type giant cells (Fig. 2*A*). Within the purulent centers of many of the tubercles were large, septate, branching hyphae containing occasional round spores. The organisms were best demonstrated by Gram stain or the Hotchkiss-McManus stain[4] (Fig. 2*B*). Between the tubercles there was a dense hyalinized connective tissue infiltrated by chronic inflammatory cells. In several areas the chronic inflammatory reaction extended into the substance of the cord for a short distance. Perivascular round cell infiltrations and degenerative changes were present throughout the cervical cord.

COMMENT

The identification of the infecting agent in this case was difficult because the body had been embalmed and therefore cultures were not taken at the time of autopsy. A study of the fungi in the tissue sections revealed both hyphae and spores, and on this basis all pathogenic fungi except Candida (Monilia), Aspergillus, and Mucor could be eliminated from consideration.[5] The large, irregular, nonseptate, branching hyphae characteristic of Mucor[6] were not found. The distinction between Candida and Aspergillus was more difficult. However, the organism was probably Aspergillus as indicated by the relatively large size of the hyphae, their prominent lateral branching, and the small number of spores.[7a]

The meninges of the cervical spinal cord were the only site of mycotic involvement. The clinical course and the histologic appearance of the granuloma suggest a long-standing chronic lesion, compatible with an origin at the time of the patient's pneumococcic meningitis. The Aspergilli are described as "weeds of culture room" and are common laboratory contaminants.[7] In this case it is possible that they were introduced into the subarachnoid space during lumbar puncture as contaminants from the skin or the needle. The fungi may even have been present in the penicillin solution injected intrathecally.

Several cases of meningeal or cerebral involvement by Aspergilli, usually as a part of generalized aspergillosis, have been reported.[8] The intrathecal penicillin and the other antibiotics administered to this patient during the treatment of her

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8. Grekin, R. H.; Cawley, E. P., and Zheutlin, B.: Generalized Aspergillosis, Arch. Path. **49**:387-392 (April) 1950. Linck, K.: Fatal Aspergillus Meningitis in Man, Arch. Path. Anat. **304**:408, 1939. Cawley.[1f]

pneumococcic meningitis probably played a role in the development of the mycotic granuloma. Antibiotic and chemotherapeutic drugs have been implicated in the development of many mycotic infections reported in the recent literature. Zimmerman [1a] reported two cases of aspergillus endocarditis occurring in patients who had prolonged administration of penicillin. Cawley [1f] described a case of pulmonary aspergillosis in which dissemination occurred after treatment with sulfonamides and penicillin. Several authors have reported cases in which moniliasis involving the tongue and the oral mucous membranes, the esophagus, the vagina, and the vulva developed during antibiotic therapy.[9] Orally administered penicillin, chloramphenicol, and aureomycin have also produced persistent diarrhea associated with heavy growths of Monilia in the stool.[10] Bronchopulmonary moniliasis occurring during antibiotic therapy has been reported.[1d]

Various factors have been considered in explanation of these mycotic complications of antibiotic therapy [1d]:

(*a*) Direct stimulation of growth on the part of antibiotics.

(*b*) Suppression of growth of bacteria and other organisms competing with the fungi in the environmental substrate.

(*c*) Change in the environmental pH as a result of change in the bacterial flora.

(*d*) Diminished host resistance to fungi as a result of vitamin deficiency or other physiopathologic factors.

With respect to Candida, Woods, Manning, and Patterson [1d] have found no in vitro stimulation or suppression of growth on the part of penicillin, chloramphenicol, or aureomycin. However, Foley and Winter [2b] found an increased mortality in chick embryos infected with Candida when these were given penicillin. Campbell and Saslaw [2a] have demonstrated in vitro enhancement of growth of Sporotrichum schenckii, Coccidioides immitis, Histoplasma capsulatum, Phialophora verrucosa, and Trichophyton mentagrophytes on the part of streptomycin.

The mechanism of the antibiotic enhancement of the growth of fungi is not known, but the possibility that the antibiotic itself is utilized by the fungi or that survivors are stimulated by metabolites made available by the lysis of antibiotic-sensitive cells is suggested by in vitro experiments with fungi and bacteria.[11]

Environmental pH changes as a factor in promoting growth of fungi in patients treated with antibiotics have not been supported by the work of Karnaky.[12] He has shown that wide variations in the pH of the media of cultures obtained from monilial vulvovaginitis do not influence the growth of the fungus.

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9. Hewitt and Williams.[1b] Mangiaracine.[1c] Woods and others.[1d] Harris.[1e]

10. Woods and others.[1d] Harris.[1e]

11. Hobby, G. L., and Dougherty, N.: Isolation of a Streptomycin-Resistant Organism Capable of Utilizing Streptomycin for Growth, Proc. Soc. Exper. Biol. & Med. **69**:544-548, 1948. Foley, G. E., and Farber, S.: Observations on the Biology of Cryptococcus Neoformans: Correlation with the Pathological Changes Observed in Three Cases of Cryptococcosis in Infants, Proc. 48th Gen. Meeting, Soc. Am. Bacteriologists **1**:66-67, 1948. Errikson, K. R.: Some Studies on the Lytic Action of Penicillin on Staphylococci and Pneumococci, Scandinav. J. Clin. & Lab. Invest. **23**:221-228, 1946.

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Harris [10] and Leitner [13] have suggested alterations in vitamin biosynthesis as a factor in lowering host resistance to fungi and have had some success in treating or preventing monilial infections during antibiotic therapy by parenteral injections of vitamin B complex.

SUMMARY

A fatal case of mycotic granuloma of the leptomeninges of the cervical spinal cord probably due to Aspergillus is presented. The clinical course simulated that of a spinal cord tumor. The fungus may have been introduced as a contaminant during treatment of the pneumococcic meningitis with intrathecal injections of penicillin three years prior to death. Evidence is cited from the literature, which indicates that the growth of the fungus was enhanced by the penicillin therapy. This complication should be added to the long list of dangers associated with the intrathecal administration of penicillin and other antibiotics.

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RACHITIC CHANGES IN VERTEBRAL BODIES

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THE WORD "rachitis" originally implied an inflammatory involvement of the vertebral column but has come to be synonymous with "rickets," a word of completely different origin. The role of rickets in the production of spinal deformities has been studied by clinical and roentgenographic methods, and some gross anatomical studies have been reported also. In the monographs on rickets by von Recklinghausen,[1] Looser,[2] Dick,[3] Hess,[4] Rabl,[5] and Vas,[6] the spinal deformities were attributed to softness of the bones and to weakness of ligamentous structures, but no histologic evidence was presented.

Van Schrick[7] reported the results of histologic examination of the vertebrae of a 1-year-old child with early scoliosis. He found broadening and disorganization of the cartilaginous columns in the proliferative zone, as well as an excessive production of osteoid tissue. Dodds and Cameron,[8] in their experiments on rats, found that the cartilages of the caudal vertebrae increased in thickness under rachitogenic conditions. Coleman, Becks, Kohl, and Copp[9] produced skeletal deformities in rats with a diet which was deficient in phosphorus but which contained adequate amounts of vitamin D. They found widening of the epiphysial cartilages of the caudal vertebrae, distortion and compression of cartilage cells, and almost complete lack of calcification, with the production of trabeculae which were made up of osteoid tissue

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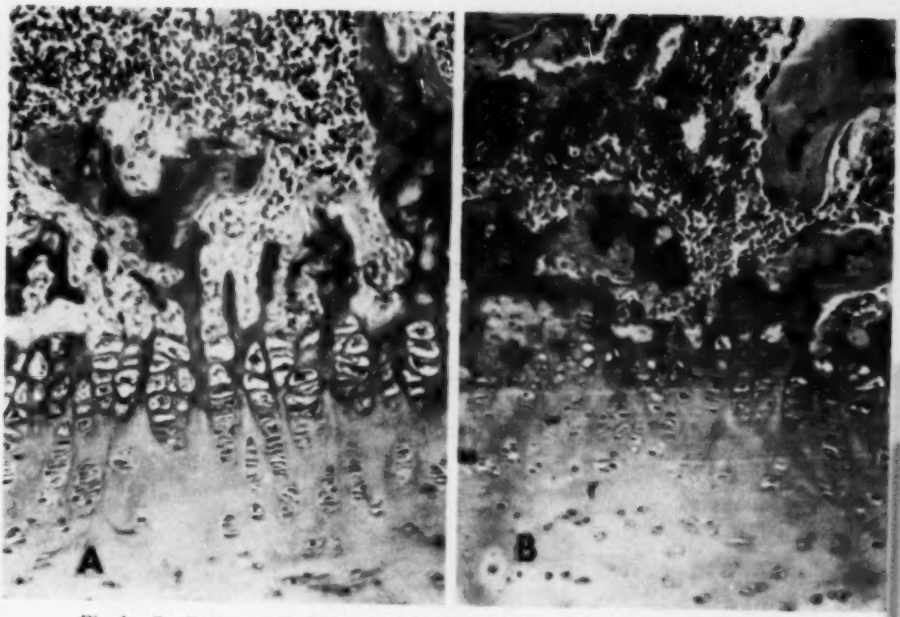

Fig. 1.—Cartilage plates of vertebral bodies from infants 3 months old. *A* is from a rachitic patient; *B*, from a nonrachitic one. The lengths of the columns of cells in the proliferating zone and the numbers of cells in the columns may be compared. × 180.

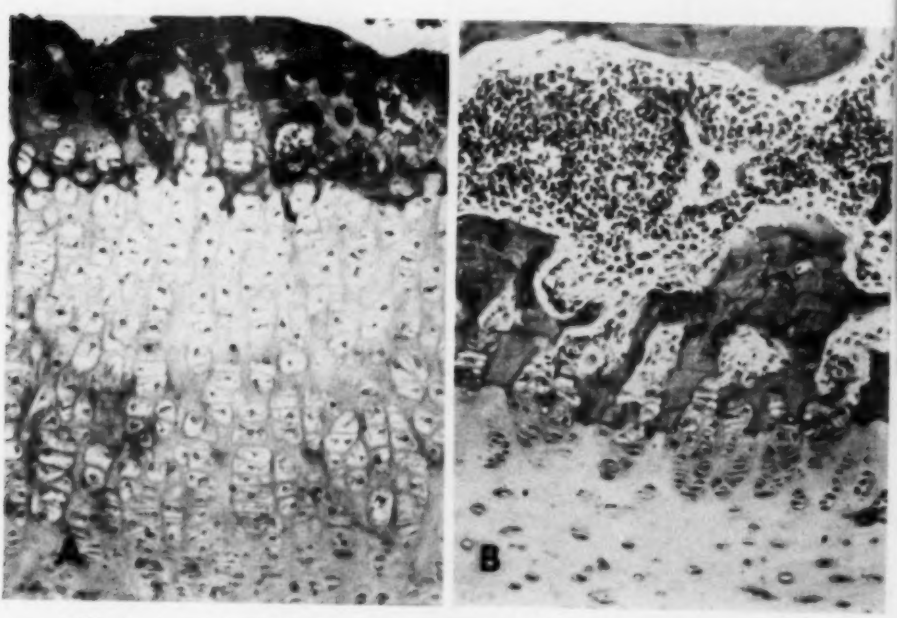

Fig. 2.—*A*, rachitic vertebra from an infant 18 months old. *B*, nonrachitic vertebra from an infant 18 months old. × 180.

and cores of cartilage. Typical rachitic changes were present in other bones. In an earlier report on a different phase of the problem of rickets, I [10] have referred briefly to the findings which form the substance of the present report.

MATERIAL

The vertebral bodies used in this study were obtained from necropsy material at the University Hospital. The cases were divided into two groups: (1) those in which costochondral junctions showing typical rachitic changes and vertebral bodies were both available and (2)

Cell Counts and Length of Cartilage Cords in Zone of Proliferation

	Rachitic Material		Nonrachitic Controls			
Age, Mo.	Cells in Cord	Cord Length, μ	Cells in Cord	Cord Length, μ	Av. No. of Cells for Age Group	Av. Cord Length for Age Group
2	10.0	266	10.2	230	....	...
	9.0	486	15.6	271	....	...
	12.0	348	14.4	266	13.4	253
2½	9.6	210	10.4	169	....	...
	....	...	9.8	174	10.1	172
3	14.4	297	9.6	184	....	...
	....	...	10.0	143	....	...
	....	...	13.8	251	....	...
	....	...	14.2	271	11.9	212
3¾	17.8	339	11.2	302	....	...
	....	...	14.4	266	....	...
	....	...	13.0	236	....	...
	....	...	12.4	230	12.8	256
4½	10.6	246	12.6	225	12.6	225
5	10.2	230	9.6	220	....	...
	....	...	10.2	210	....	...
	....	...	12.2	220	....	...
	....	...	9.0	189	....	...
	....	...	9.0	297	10.0	259
6	12.6	304	10.2	230	....	...
	16.6	334	10.0	185	....	...
	13.8	348	9.4	154	....	...
	....	...	10.0	241	9.9	206
8	20.0	527	9.6	133	....	...
	12.4	271	12.0	240	....	...
	16.0	415	12.2	261	11.3	212
9	20.0	455	15.0	230	....	...
	12.6	246	12.6	246	....	...
	....	...	10.8	184	....	...
	....	...	14.2	287	....	...
	....	...	8.4	164	12.2	222
10	9.4	235	7.6	128	....	...
	....	...	11.2	206	....	...
	....	...	6.8	138	8.5	156
18	12.0	246	10.4	164	....	...
	....	...	9.8	210	....	...
	....	...	9.6	159	....	...
	....	...	9.6	128	9.9	165

those in which the costochondral junctions showed no rachitic change and the vertebral bodies could be studied as controls. These nonrachitic controls were selected at random from the necropsy material, except that cases with any skeletal abnormality were excluded. None of the infants in either group showed clinical or gross pathologic evidence of vertebral involvement. The primary illnesses of the infants from whom these two groups of bones were obtained are summarized as follows.

Cases Supplying Rachitic Material.—Congenital biliary stenosis, including all obstructive anomalies, 8 cases; internal hydrocephalus, prematurity with malnutrition, hemangioblastoma, hepatic lipoidosis, hepatitis of undetermined cause, lipid pneumonia, lobar pneumonia, virus pneumonia, pertussis, intestinal obstruction, 1 case of each.

10. Hendrix, R. C.: Osseous Changes in Congenital Biliary Stenosis, A. M. A. Arch. Path. **51**:518 (May) 1951.

Cases Supplying Control Material.—Pneumonitis of all types, 6 cases; congenital heart disease, 5 cases; enterocolitis, 4 cases; laryngotracheobronchitis, 4 cases; diarrhea, 3 cases; congenital urinary tract obstruction, pneumococcic meningitis, miliary tuberculosis, internal hydrocephalus, and anemias of all types, 2 cases each; cheiloschisis (anesthetic death), lymphangioma coili (operative death), intracerebral lymphangioma, subarachnoid hemorrhage, birth trauma, asphyxia (smoke), and Letterer-Siwe disease, 1 case each.

The bones were decalcified by the formic acid technique and stained with hematoxylin and eosin.

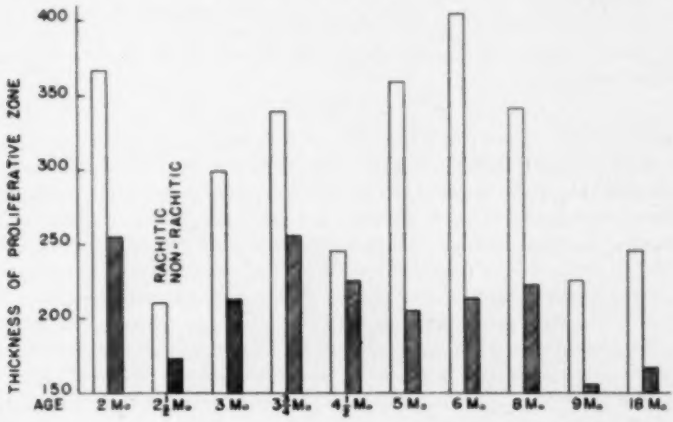

Fig. 3.—Graphic comparison of the thicknesses of the proliferative zones of rachitic and nonrachitic vertebral bodies. Where several rachitic cartilages have been measured, the values have been averaged. The values are derived from the table. Thickness is expressed in microns.

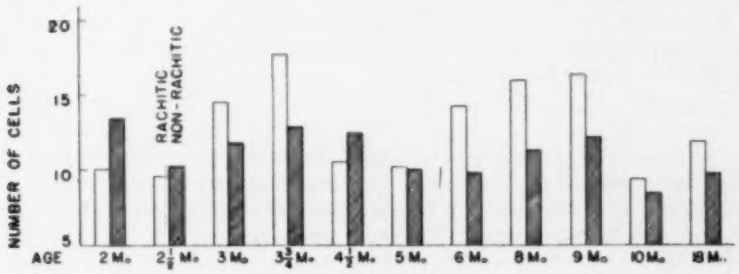

Fig. 4.—A graph of the numbers of cells in the proliferative zones in rachitic and nonrachitic vertebrae, for comparison with Figure 3. The values are derived from the table.

OBSERVATIONS

Comparison of sections of rachitic and nonrachitic vertebrae showed that in the former the proliferating zone of the epiphysial plate was increased in thickness and appeared to contain a greater number of cells (Figs. 1 and 2). In substantiation of these features, measurements by ocular micrometer and cell counts were made at five locations selected at random on each specimen. These were averaged. The averages for each of the control readings in a given age group were again averaged

to minimize individual variation, and the resulting figures were compared with those obtained from the rachitic group. These data are presented in the accompanying table, and shown graphically in Figures 3 and 4.

It is to be noted that although these values normally increase with increasing age, the differences between the cartilaginous cell columns of rachitic and nonrachitic patients are not only maintained but accentuated with increasing age. The figures for occasional cases do not fit perfectly into this ascending scheme, but the over-all differences are obvious.

In sections which had not been decalcified excessively it was possible to note that the osteoid borders of the trabeculae were thicker in the rachitic than in the nonrachitic vertebrae.

COMMENT

In addition to the poor calcification of the trabeculae and the excessive production of osteoid tissue, changes of the cartilage of the epiphysial plate would be expected, since the disturbance in rickets is largely that of defective calcification of proliferating cartilage. It is well known that the resulting defect is striking in the costochondral junction, where a conspicuous overgrowth and deformity of the cartilage plate is produced. A comparable deformity was not observed in the vertebral bodies of the rachitic material used in this study. Van Schrick[3] described disorganization of the columns of cartilage cells in a case of scoliosis. Presumably, in none of the cases in the present report was the disturbance as far advanced, since none of the infants showed scoliosis. The line of provisional calcification was straight, the columns of cartilage cells were regular, and there were no invasive capillary "bushes" in the cartilage plate. It seems, however, that the observed increase in lengths of the columns and the increase in the numbers of cells in the columns reflect a failure of calcification and subsequent destruction of cartilage just as in the costochondral junction.

A histologic study of obviously deformed vertebral bodies would be of interest. Since these were not available from human material, a similar study on experimental rickets in rats is now in progress.

SUMMARY

The columns of proliferating cartilage in the epiphysial plates of rachitic vertebrae were measured, and the cells in these columns were counted. The values thus obtained were compared with similar values obtained from nonrachitic vertebrae and were almost uniformly greater for the rachitic tissues. The differences between the two groups tended to increase with increasing age. The process is similar to that described for the ribs and long bones of the extremities, but at comparable stages the same degree of deformity is not produced in the vertebral bodies.

ALKALINE PHOSPHATASE ACTIVITY OF THE KIDNEY

Following Experimental Shock in Dogs Induced by Clostridium Perfringens Toxin

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AND
S. A. LEVINSON, M.D.
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IN A RECENT communication [1] we reported the effect which Clostridium perfringens has on the kidneys of dogs in experimental shock. In the present study we wish to report the changes of the alkaline phosphatase activity and their correlation with the mitochondrial alterations, and the excretion of phenol red in the proximal convoluted tubules.

Recent reports have indicated that the alkaline phosphatase is altered by nephrotoxic drugs.[2] Menton and Janouch [3] observed a reduction of alkaline phosphatase in the brush border of the proximal convoluted tubules following alloxan administration and a diffusion of the enzyme in the mitochondria of contiguous cells. This redistribution was not observed with the higher doses of alloxan. They also observed alterations in the mitochondrial structure. Wachstein [4] reported that following the injection of dl-serine in rats, necrosis developed in the distal portion of the proximal convoluted tubules, with a uniform deep-staining alkaline phosphatase reaction in the involved cells. In animals receiving lethal doses of mercury bichloride and uranyl nitrate, according to Simonds and Hepler,[2] the phosphatase was sharply reduced in the completely necrotic straight terminal portions of the tubules, while it was unaffected in the remaining uninvolved portion of the proximal convoluted tubules. These authors observed that with smaller doses the phosphatase was found distributed throughout the necrotic cells of the distal portion of the proximal convoluted tubules. They also demonstrated that potassium dichromate affected the renal phosphatase in much the same way as mercury bichloride, with the phosphatase appearing to be abundant throughout the necrotic cells. Minimal doses affected the first part of the proximal convoluted tubules and large doses the entire tubule.

From the University of Illinois Research and Educational Hospital Laboratory, and the Departments of Medicine and Pathology, University of Illinois College of Medicine.

1. Berg, M.; Levinson, S. A., and Wang, K. J.: Effect of Experimental Shock Induced by Clostridium Perfringens Toxin on the Kidneys of Dogs, A. M. A. Arch. Path. **51**:137 (Feb.) 1951.

2. Simonds, J. P., and Hepler, O. E.: Experimental Nephropathies: IX. A Summary of Experiments on Dogs, Quart. Bull. Northwestern Univ. M. School **19**:278, 1945.

3. Menton, M. L., and Janouch, M.: Changes in Alkaline Phosphatase of the Kidney Following Renal Damage with Alloxan, Proc. Soc. Exper. Biol. & Med. **63**:33, 1946.

4. Wachstein, M.: Nephrotoxic Action of dl-Serine in Rat, Localization of Renal Damage, Phosphatase Activity and Influence of Age, Sex, Time and Dose, Arch. Path. **43**:503, 1947.

Novikoff [5] has recently questioned the validity of the present methods of localizing intracellular phosphatase activity. Feigin, Wolf, and Kabat [6] have presented evidence that the nuclear staining surrounding foci of intense phosphatase activity, demonstrated histochemically by the Gomori technique, may be an artifact under some circumstances due possibly to the diffusion of the enzyme after death. Newman, Feigin, Wolf, and Kabat [7] described three groups of phosphatases based on substrate specificity rate of hydrolysis, effect of inhibitors, and activities and differences in site of occurrence. The validity of the three groups of phosphatase has been questioned by Novikoff [5] on the basis of his recent experiments.

EXPERIMENTS

Three groups of dogs were studied as previously reported.[1] A lethal dose of Clostridium perfringens toxin [8] (8 ml. per kilogram of body weight) was injected intramuscularly into the midportion of the hindleg in the first group of animals. In the second group the injected hindleg was massaged in order to increase the rate of diffusion of the toxin. The third group of animals was used as a control and did not receive the toxin. The animals that received the toxin were killed at half-hourly intervals, and representative sections were taken immediately from various organs for histologic and histochemical study. Before being killed, the animals were given injections of sodium ferrocyanide and phenol red (phenolsulfonphthalein). It has been previously shown [9] that the ferrocyanide is filtered through the glomeruli and that the phenol red [10] is secreted (85%) by the proximal convoluted tubules. Specimens for histochemical study were fixed in cold acetone, and, after they had been rapidly frozen and dehydrated by the method of Gersh and Bensley,[11] they were sectioned, and the sections were mounted on a slide, incubated for one hour, and stained according to Gomori's [12] technique for alkaline phosphatase. In addition, specimens were fixed in Regaud's fluid, alcohol, and formaldehyde solution.

OBSERVATIONS

Lethal doses of Cl. perfringens toxin injected intramuscularly produced extensive edema at the sites of injection and consequent hemoconcentration. This was accompanied by an increase in the urea nitrogen and a reduction in the chloride of the blood, while the alkaline phosphatase and the potassium remained unchanged. Although the blood pressure was not significantly altered in the first hour, there was a marked reduction in the volume of the urine output one hour after injection, and abnormal urinary sediments were present.

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5. Novikoff, A. B.: The Validity of Histochemical Phosphatase Methods on the Intracellular Level, Science **113**:320, 1951.

6. Feigin, I.; Wolf, A., and Kabat, E. A.: Histochemical Studies on Tissue Enzymes: VI. A Difficulty in the Histochemical Localization of Alkaline Phosphatase in Nuclei, Am. J. Path. **26**:647, 1950.

7. Newman, W.; Feigin, I.; Wolf, A., and Kabat, E. A.: Histochemical Studies on Tissue Enzymes: IV. Distribution of Some Enzyme Systems Which Liberate Phosphate at pH 9.2 as Determined with Various Substrates and Inhibitors; Demonstration of Three Groups of Enzymes, Am. J. Path. **26**:257, 1950.

8. The toxin was furnished by Eli Lilly & Company, Indianapolis.

9. Gersh, I., and Steiglitz, E. J.: Histochemical Studies on Mammalian Kidney: Glomerular Elimination of Ferrocyanide in Rabbit, and Some Related Problems, Anat. Rec. **58**:349, 1934.

10. Gersh, I.: Tubular Elimination of Phenol Red in Rabbit Kidney, Am. J. Physiol. **108**:355, 1934.

11. Gersh, I.: Altman Technique for Fixation by Drying, While Freezing, Anat. Rec. **53**:309, 1932.

12. Gomori, G.: Study of Enzymes in Tissue Sections, Am. J. Clin. Path. **16**:347, 1946.

Histologic examination of the kidneys of the group of animals that received the injection of the toxin without massage revealed a gradually increasing number of glomeruli with evidence of vasoconstriction and swelling of the glomerular tufts. This was first manifested two and one-half hours after injection and was most pronounced at the end of four hours. There was definite reduction in the amount of the ferrocyanide filtered through the constricted capillaries of the swollen glomeruli. Concomitantly there was widespread constriction of the cortical arterioles and capillaries. Four and one-half to five hours after injection of the toxin there were wide dilatation of the glomerular capillaries, reduction in the size of the tufts, and generalized vascular congestion, which reflected the increasing circulatory failure. There was also an accompanying increase in the glomerular filtration of the ferrocyanide.

We compared the phosphatase activity demonstrated when we used the cold acetone fixation technique with that revealed when the freezing-drying method was used, and observed a greater concentration of phosphatase when using the latter method. There was less structural distortion with the freezing-drying fixation than with the cold acetone technique. Losses due to fixation, dehydration, and embedding have been reported by Stafford and Atkinson,[13] Danielli,[14] and others.[15] The phosphatase activity was distinctly more pronounced with the freezing-drying fixation, and considerable phosphatase activity was observed in many of the glomeruli. This activity was seen in all parts of the affected glomeruli. On the other hand, many of the glomeruli showed little to no phosphatase activity, particularly those further removed from areas of high phosphatase activity (proximal tubules).

Since adsorption artifacts occur readily during the Gomori procedure (Novikoff), conclusions concerning the high alkaline phosphatase activity of some tissues demand careful scrutiny. Contrary to Danielli's[14] conclusion, Novikoff [5] observed that cytologic sites of high calcium phosphate adsorption and high alkaline phosphatase activity do not coincide. The apparent diffusion and adsorption ascribed to nuclei have been noted by a number of writers and were demonstrated experimentally by Martin and Jacoby,[15b] who pointed out that nuclear staining is of dubious significance, because it occurs adjacent to areas of high phosphatase activity. It is not clearly established whether it is calcium phosphate or enzyme or both which diffuse from regions of high alkaline phosphatase activity, although in reporting recent experiments Gomori [16] attributed considerably less significance to enzyme adsorption as compared with calcium phosphate adsorption.

Abnormal phosphatase activity was not observed in the proximal convoluted tubules in our series of toxin-affected animals until four hours after the toxin was

13. Stafford, R. W., and Atkinson, W. B.: Effect of Acetone and Alcohol Fixation and Paraffin Embedding on Activity of Acid and Alkaline Phosphatases in Rat Tissues, Science **107**:279, 1948.

14. Danielli, J. F.: A Critical Study of Techniques for Determining the Cytological Position of Alkaline Phosphatase, J. Exper. Biol. **22**:110, 1946.

15. (*a*) Emmel, V. M.: The Intracellular Distribution of Alkaline Phosphatase Activity Following Various Methods of Histologic Fixation, Anat. Rec. **95**:159, 1946. (*b*) Martin, B. F., and Jacoby, F.: Diffusion Phenomenon Complicating the Histochemical Reaction for Alkaline Phosphatase, J. Anat. **83**:351, 1949.

16. Gomori, G.: Sources of Error in Enzymatic Histochemistry, J. Lab. & Clin. Med. **35**:802, 1950.

injected. This series was characterized by a conspicuous reduction or absence of phosphatase activity in the brush border of a number of the involved cells. A considerable variation was observed in the amount of activity. Many of the cells in the proximal convoluted tubules revealed normal phosphatase activity, and in others there was reduced activity (Fig. 1*A*). This variability was quite striking when contrasted with the normal (Fig. 1*B*). Considerable variation was noted in the phosphatase response from animal to animal in the experimental series. In some of the animals killed four hours after toxin injection the number of tubules with reduced phosphatase activity was much greater than in animals killed five hours after injection of toxin.

The earliest intracellular histologic alteration was manifested in the mitochondria of the proximal convoluted tubules, and there was considerable variation in the degree of involvement from cell to cell. In the later specimens (five hours after injection of toxin) the degree of mitochondrial involvement was greatly increased, and in the severely involved areas one could observe some normal cells and normal-appearing mitochondria adjacent to the abnormal ones. The histochemical studies employing phenol red, which is excreted chiefly by the proximal convoluted tubules, also demonstrated that not all of the cells in the kidney were uniformly involved. In the early stages (one to two hours after injection of the toxin) some of the tubules were more involved than others, and in the later stages (four to five hours) practically all the tubules were affected and failed to secrete the dye within their cells.

In a second group of animals that had received the toxin and massage of the injected extremity, the kidneys that were removed four hours after the injection revealed a pronounced and uniform reduction of phosphatase activity (Fig. 2*A*). The amount of reduction was quite striking when the activity was compared with the normal (Fig. 2*B*). Histologic examination of the kidney revealed swelling of a large number of the glomerular tufts, and, in addition, presence of hemoglobin in Bowman's space. Hemoglobin was also observed in some of the capillaries. Many of the proximal convoluted tubules presented a normal appearance, while others showed varying degrees of cloudy swelling and vacuolation. In some of the tubules, small globules of hemoglobin had been absorbed within the cells. One of the most striking alterations noted was the severe and diffuse changes in the mitochondria. In many cells of the proximal tubule the mitochondria were disintegrated or absent; in others they appeared in clumps. The injected phenol red was not deposited in the proximal convoluted tubules.

The changes in the blood pressure, the urea nitrogen and chlorides of the blood, and the hemoconcentration were essentially similar in both experimental groups of animals. One significant variation was the increased rate of hemolysis in the animals receiving toxin and massage. There was an increase in the numbers of casts, erythrocytes, leucocytes and amorphous granules and in the debris in the urine.

In both groups of dogs which had received the toxin, the histologic examination of the liver and the alkaline phosphatase reaction showed no apparent abnormality.

COMMENT

The mechanism of action of the Cl. perfringens toxin injected intramuscularly or intravenously into dogs may represent a combination of factors: (1) There is

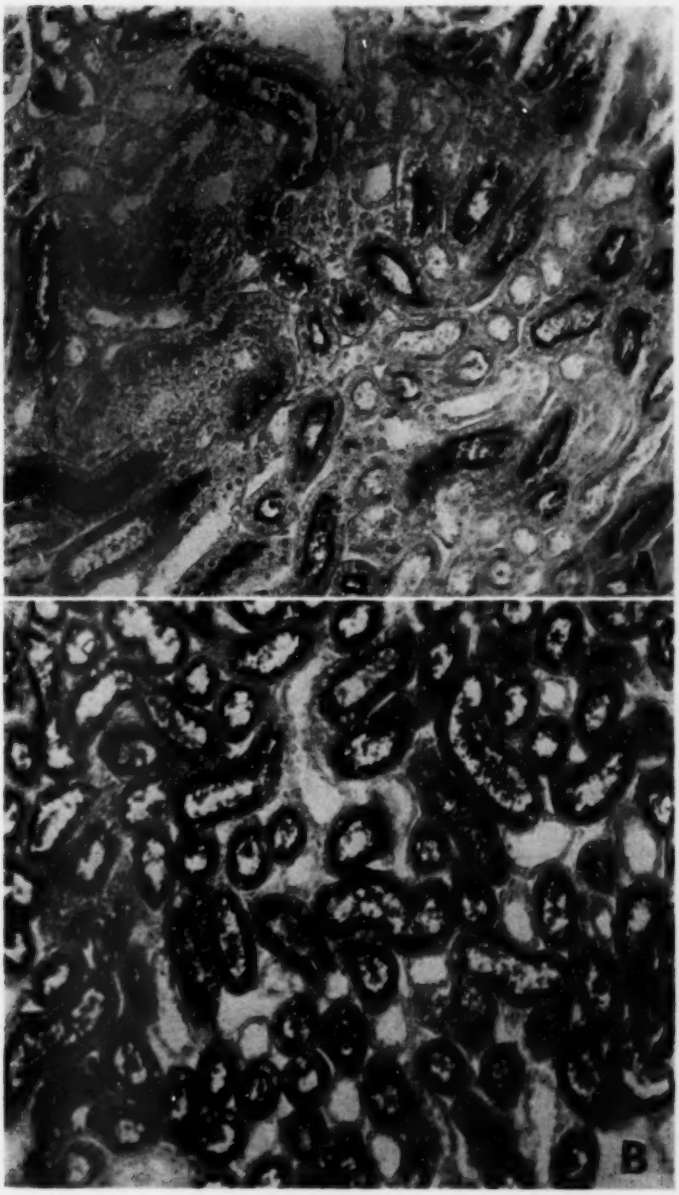

Fig. 1.—*A*, kidney removed four hours after injection of toxin, showing the variation in the reduction of alkaline phosphatase activity in the brush border of the proximal convoluted tubules. *B*, kidney from a control animal, showing the normal-appearing alkaline phosphatase activity in the proximal convoluted tubules.

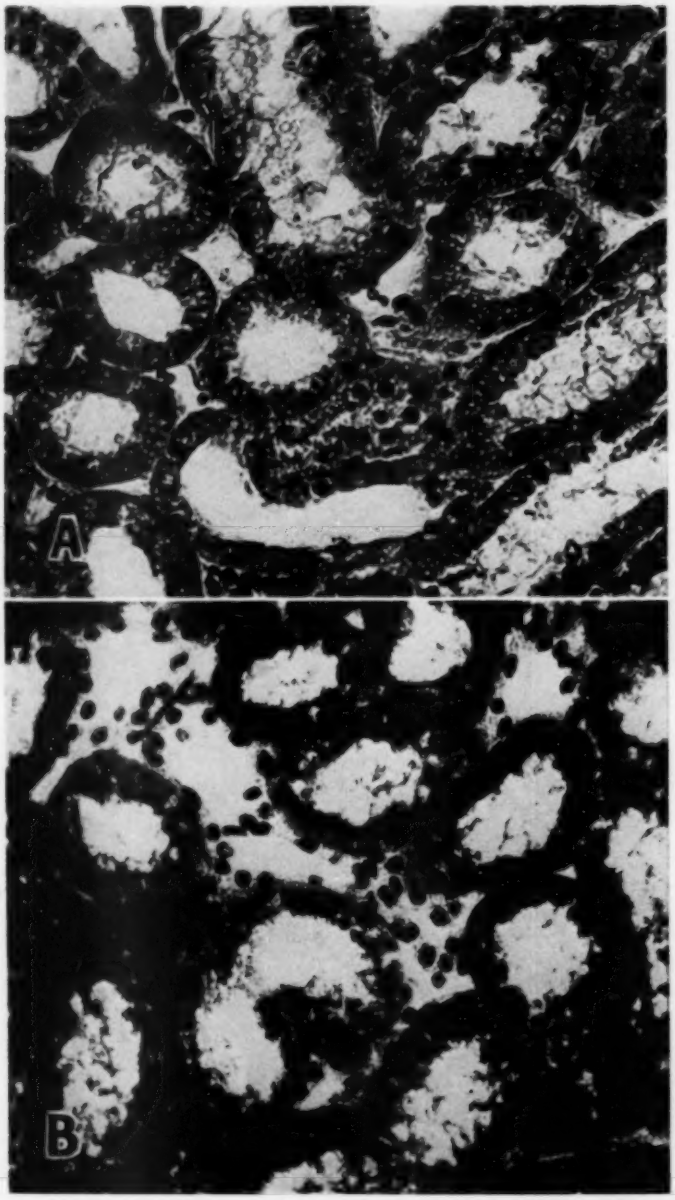

Fig. 2.—*A*, kidney removed four hours after injection of toxin and massage of the site of injection. Note the uniform severe reduction of alkaline phosphatase activity in the brush border of the proximal convoluted tubules. (Section counterstained with hematoxylin and eosin.) *B*, kidney from a control animal, showing the normal-appearing alkaline phosphatase activity in the proximal convoluted tubules. (Section counterstained with hematoxylin and eosin.)

a lecithinase component,[17] which appears to act on the phosphatides of cell surfaces, hemolyzing erythrocytes and affecting or destroying tissue cells; (2) the combination of a lecithinase and a hyaluronidase component [18] (plus small amounts of unknown toxin) may result in an edema-forming power, and (3) there is the possibility that all the effects obtained are not due to the direct action of the toxin alone but may be ascribed in part to the products of tissue breakdown.[19] The histologic intracellular changes which were noted in the mitochondria were the earliest manifestations of cellular alterations. Injection of the toxin followed by massage was accompanied by increased hemolysis and by diffuse and severe intracellular disintegration of the mitochondria, as well as by an absence of deposit of phenol red within the cells. There was a widespread reduction of the alkaline phosphatase activity in the affected cells. The changes in the cellular physiology were more readily detected with histochemical staining methods than with hematoxylin and eosin stains. The altered function of the cells was accompanied by the reduction in enzyme activity and intracellular destruction, probably due to the alteration of cellular activity resulting from the effects of the Cl. perfringens toxin. This was reflected in the early appearance of abnormal urinary constituents. Stowell and Lee [20] have shown that the toxic action of carbon tetrachloride affects the cellular activity of the liver and that there is a decrease of different enzymes (including alkaline phosphatase) and cellular substances in the early stages.

In the animals that received the injection of toxin without massage, the pattern of development of the renal alterations was different. While the intracellular alterations of the mitochondria were among the earliest observed, these at first involved scattered cells of the proximal convoluted tubules. In the specimens obtained some hours after injection of the toxin, more severely affected areas were encountered. Even in areas that were extensively and actively involved there was persistence of cells that appeared normal or nearly normal. In the proximal convoluted tubules there was an apparent correlation between the structural appearance of the mitochondria and the function of the tubules as indicated by the secretion of phenol red. The amount of dye secreted appeared to bear an inverse ratio to the severity of the mitochondrial alterations.

In addition, the reduction of alkaline phosphatase activity in general appeared to parallel the mitochondrial changes. There was considerable variation in alkaline phosphatase activity from cell to cell. The changes were not uniform in relation to the degree of structural changes, as some of the earlier specimens showed a

17. Glenny, L. T.; Barr, M.; Llewellyn-Jones, M.; Dalling, T., and Ross, H. E.: Multiple Toxins Produced by Organisms of Clostridium Welchii Group, J. Path. & Bact. **37**:53, 1933. Zamecnik, P. C.; Folch, J., and Brewster, L.: Protection of Animal Against Clostridium Welchii (Type A) Toxin by Injections of Certain Purified Lipids, Proc. Soc. Exper. Biol. & Med. **60**:33, 1945.

18. (*a*) McLean, D., and Hale, C. W.: Study on Diffusing Factors: The Hyaluronidase Activity of Testicular Extracts, Bacterial Culture Filtrates and Other Agents That Increase Tissue Permeability, J. Biochem. **35**:159, 1941. (*b*) Oakley, C. L.: The Toxins of Clostridium Welchii: Critical Review, Bull. Hyg. **18**:781, 1943. (*c*) MacFarlane, R. G., and MacLennon, J. D.: The Toxemia of Gas Gangrene, Lancet **2**:328, 1945.

19. MacLennon, J. D., and MacFarlane, R. G.: Toxin and Antitoxin Studies of Gas Gangrene in Men, Lancet **2**:301, 1945. MacFarlane and MacLennon.[18c]

20. Stowell, R. E., and Lee, C. S.: Histochemical Studies of Mouse Liver After Single Feedings of Carbon Tetrachloride, Arch. Path. **50**:519 (Nov.) 1950.

greater degree of reduction of phosphatase than the later ones. This may have been due to variations in individual susceptibility or to the relatively large magnitude of phosphatase alteration (before becoming apparent with the methods presently available) or to a combination of these factors.

The sequence of glomerular and tubular alterations following intramuscular injections of Cl. perfringens toxin suggests that the action may be the result of (1) circulatory alterations, (2) the direct action of the toxin or toxic products on the cells, or (3) a combination of these factors. In the group of animals that received massage in addition to injection of the toxin, the differences observed may be the result of the toxic action of the increased amounts of hemoglobin pigment absorbed by the tubules or the presence, in addition to the other toxic factors, of increased amounts of lecithinase and its action on cell surfaces.

Our observations on the alkaline phosphatase alterations differ in a number of respects from those reported in the literature.[21] This difference may be due to the difference of the toxic agents employed and of their selective affinity for the kidney. Wachstein [4] injected *dl*-serine into mice and noted a uniform alkaline phosphatase staining reaction of cells of the distal portion of the proximal convoluted tubules. Potassium dichromate, too, has been reported [2] to have precisely this same effect. On the other hand, mercury bichloride and uranyl nitrate have been observed to effect a definite reduction of the alkaline phosphatase activity in the necrotic straight terminal portion of the proximal convoluted tubules. With smaller doses the phosphatase was found diffused throughout these cells. A reduction of alkaline phosphatase activity has been observed in the brush border following alloxan administration.[3] Differences have been observed in alkaline phosphatase activity on comparing the freezing-drying fixation with the cold acetone fixation, as reported by others.[22] The decrease of activity in the sections of kidney and liver fixed in cold acetone as compared with tissues given freezing-drying fixation, and the structural distortion, have been noted and discussed above.

SUMMARY

The histochemical and cytologic observations in conjunction with the physiologic and chemical studies of the blood and urine provide a composite picture of the cellular changes of the kidney associated with experimental shock induced by lethal doses of Clostridium perfringens toxin.

A sequence of functional and structural alterations of both the glomeruli and the tubules was observed which suggested that the effects of the toxin on the kidneys may be the result of (1) circulatory changes, (2) a direct action of the toxin or toxic products on the cells, or (3) a combination of these factors.

The changes in cellular physiology were more readily detected with the histochemical and mitochondrial staining method than with the hematoxylin and eosin stain.

The reduction of the alkaline phosphatase activity, the intracellular destruction, and the effect on the secretion of phenol red are probably due to the alteration of cellular activity resulting from the toxic effect of the Cl. perfringens toxin.

808 S. Wood St.

21. Simonds and Hepler.[2] Menton and Janouch.[3] Wachstein.[4]
22. Stafford and Atkinson.[12] Danielli.[14] Emmel.[15a] Martin and Jacoby.[15b]

Case Reports

CORONARY BLOOD VESSEL ARISING FROM CARDIAC VENTRICLE

Report of a Case Showing Other Cardiac Anomalies

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REGINA, SASK., CANADA

A NUMBER of congenital malformations of the coronary blood vessels have been described, but there are very few records of coronary vessels communicating directly with the cavities of the ventricles.

This report describes a case of congenital heart disease in which pulmonary valvular atresia and a patent interventricular septum were associated with a large vessel running between the right ventricle and the main trunk of the left coronary artery.

CASE HISTORY

The patient was a newly born female infant who lived only 36 hours after delivery. The mother had two previous pregnancies, and the two children therefrom were living and healthy. She herself had been in good health throughout the pregnancy. Delivery occurred at term, and labor was uneventful.

AUTOPSY REPORT

The body was that of a newly born female infant. The weight was 2,350 gm.; the length (crown-heel), 30 cm. The body was deeply cyanosed.

Cardiovascular System.—The pericardial cavity contained a few milliliters of clear fluid.

The heart was slightly enlarged. The sternocostal surface was occupied by the left ventricle, and no distinct anterior interventricular groove was visible. This feature was accentuated by the absence of an anterior descending branch of the left coronary artery. Commencing on the anterior surface of the left ventricle and arising from the left coronary artery about 1 cm. from the origin of the latter was a prominent epicardial vessel at least as large as the left coronary artery. This vessel ran obliquely to the right and slightly toward the apex and disappeared into the cardiac wall along the right border of the ventricle. Shortly after it took origin from the left coronary artery this anomalous vessel was thickened by a fusiform yellow plaque, which narrowed the lumen slightly (Fig. 1).

The total length of the subepicardial portion of this vessel was 1 cm. This vessel was opened along its length, and the continuity of its lumen with that of the left coronary artery was established (Fig. *2B*). At its right end the vessel communicated through a sinusoidal channel with the cavity of the rudimentary right ventricle (Fig. *2A*).

On dissecting the heart the right ventricle was found to occupy a ridge on the right border of the large left ventricle. The cavity of the right ventricle was small,

From Pathological Laboratory, Regina Grey Nuns' Hospital

Fig. 1.—Anterior surface of the heart and great vessels, showing anomalous vessel (arrow) running into the myocardium after a short subepicardial course.

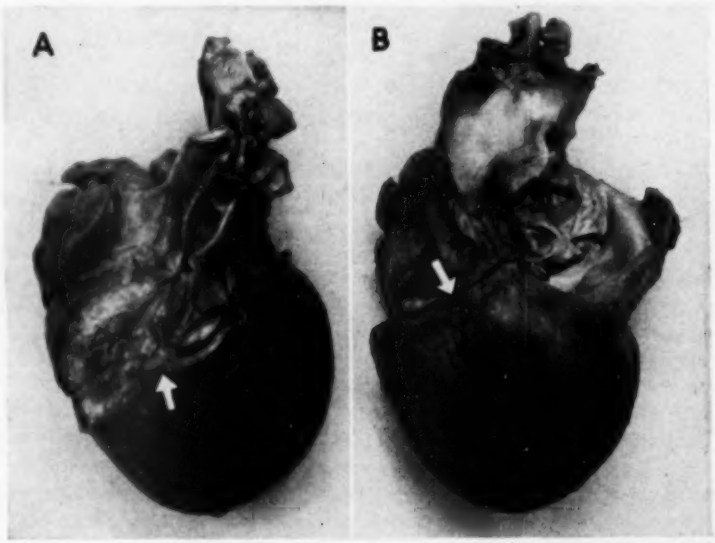


Fig. 2.—*A*, anterior surface of the heart with the right ventricle displayed. This shows right ventricular hypertrophy, pulmonary valve atresia, and the ventricular opening of the anomalous coronary vessel (point of arrow). *B*, anterior surface of the heart viewed from the left, showing the left coronary artery opened along its length. The anomalous vessel is also opened running transversely toward the right ventricle (left in photograph). The cut surface of the lipoid plaque is shown.

but its muscle was hypertrophied (Fig. 2*A*). The pulmonary conus and the origin of the pulmonary trunk were greatly narrowed to the point of obliteration of the lumen proximal to the valve ring (Fig. 2*A*). The pulmonary artery above the valve ring was well developed and was in normal relationship with the aorta. The ductus arteriosus was patent and of normal size. The right atrium appeared normal, but the right atrioventricular orifice was small and the valves were rudimentary.

The left atrium was normal, and the atrioventricular valves were normal. The left ventricle was considerably enlarged, owing to dilatation and hypertrophy. The interventricular septum was patent in its upper portion, but the defect was of small diameter (2 mm.).

The left coronary artery arose from the left aortic sinus and followed its normal course for a distance of 1 cm., where the anomalous vessel took origin (Fig. 2*A*). Beyond this point the left coronary system was represented by a number of fine branches, which radiated across the left ventricle.

The right coronary artery was of very small caliber and had only a pinpoint ostium in the normal situation in the right aortic sinus.

No significant abnormalities were discovered in the dissection of the other systems.

COMMENT

In the presence of complete pulmonary atresia it would appear that the pressure within the right ventricle during systole must have been sufficient to cause dilatation of the intramural embryonal sinusoids with ultimate retention and molding of anastomotic channels between these sinusoids and the coronary circulation. In this case the anastomotic channels have become particularly well defined. A similar case was encountered by Williams, Kent, and Edwards.[1] In their case an anastomotic channel, part of which had the structure of a modified embryonal sinusoid and part the structure of a coronary vessel, ran from the right ventricle to the posterior descending branch of the right coronary artery. Their case also showed atresia of the pulmonary valve but did not have an interventricular septal defect. Edwards,[2] who examined the heart from our case, considered the interventricular septal defect present so small that the mechanism responsible for the development of this channel was similar to that postulated for their case.[2]

A number of authors have described persistent embryonal sinusoids in the myocardium and have shown communications between these sinusoids and the coronary circulation. As far as we can determine the case described by Williams, Kent, and Edwards [1] and the case described in this report are the only ones in which the communication could be described as an anomalous cardiac blood vessel. The significant etiological factors common to these cases appears to be pulmonary valvular atresia. It seems likely that a large interventricular septal defect might prevent the development of such a channel by permitting the escape of blood from the right ventricle during systole.

1. Williams, R. R.; Kent, G. B. Jr., and Edwards, J. E.: Anomalous Cardiac Blood Vessel Communicating with the Right Ventricle: Observations in a Case of Pulmonary Atresia with an Intact Ventricular Septum. A. M. A. Arch. Path. **52**:480-487 (Nov.) 1951.

2. Edwards, J. E.: Personal communication to the authors.

SUMMARY

A case of congenital heart disease is described in which the major defects were pulmonary valvular atresia and a small interventricular septal defect. An anomalous coronary vessel was found arising from the lumen of the right ventricle and communicating with the left coronary artery. It is suggested that this vessel developed as a result of high pressure in the right ventricle during systole, causing retention of an anastomosis between intramural sinusoids and the coronary circulation and elaboration of this connection into a grossly recognizable vessel. Such a communication would permit some escape of blood from the right ventricle, since the pulmonary valvular atresia is apparently complete.

Dr. J. E. Edwards, of the Mayo Clinic, Rochester, Minn., examined this specimen and gave us permission for the reproduction of his photographs of the specimen, shown in Figure 2.

AORTIC ORIGIN OF THE RIGHT PULMONARY ARTERY AND ABSENCE OF THE TRANSVERSE AORTIC ARCH

Associated with Patency of the Interventricular Septum and the Ductus Arteriosus

EDWARD W. JEW Jr., B.S.
AND
PAUL GROSS, M.D.
PITTSBURGH

CONGENITAL absence of the transverse aortic arch is quite rare. Weisman and Kesten [1] have recently reviewed the literature concerning this anomaly and were able to list only 14 cases, including one of their own. No additional cases have been found subsequent to this review.

The aberrant origin of a pulmonary artery is likewise uncommon, and its origin from the ascending or the transverse arch is excessively rare, with only four cases presented in the literature. In the case reported by Fraentzel [2] the right pulmonary artery took origin from the aorta just proximal to the arch, while in the case described by Thomas [3] the left pulmonary artery arose from the transverse arch immediately to the left of the left innominate artery. Two of these cases, those of Doering [4] and Ambrus,[5] are similar except that the right pulmonary artery arose from the right innominate artery. Because of identical embryologic pathogenesis it would appear proper to classify the latter two cases with those in which the pulmonary artery takes origin from the transverse aortic arch.

There are, in addition, a fair number of cases reported under the heading of absence of the pulmonary artery. In such instances the pulmonary artery is associated with a common truncus arteriosus or arises from a subbranch of one of the main vessels of the aorta.

It is the purpose of this paper to describe a case in which absence of the transverse aortic arch coexisted with origin of the right pulmonary artery from the ascending aorta, a combination which hitherto has apparently not been reported.

From the Laboratory of Clinical Pathology, St. Joseph's Hospital.

Mr. Jew is Junior Student in the University of Pittsburgh School of Medicine.

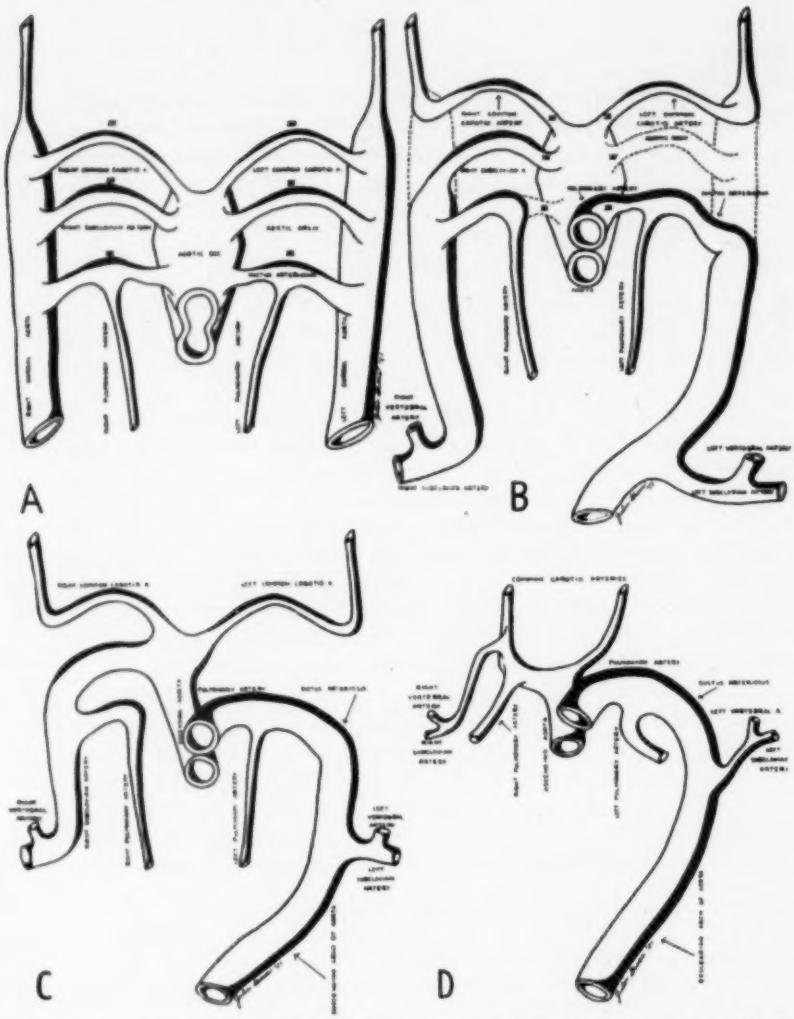
1. Weisman, D., and H. D. Kesten: Absence of Transverse Aortic Arch with Defects of Cardiac Septums: Report of a Case Simulating Acute Abdominal Disease in a Newborn Infant, Am. J. Dis. Child. **76**:326 (Sept.) 1948.

2. Fraentzel, O.: Angeborener Defect der rechten Lungenarterie, Arch. path. Anat. **43**:420, 1868.

3. Thomas, H. W.: Congenital Cardiac Malformations, J. Tech. Methods **21**:58, 1941.

4. Doering, H.: Angeborener Defect der rechten Lungenarterie, Studien Path. Entwicklung **2**:41, 1914.

5. Ambrus, G.: Absence of the Right Pulmonary Artery and Replacement by Anomalous Branch from Innominate Artery and Bleeding into the Right Lung, J. Tech. Methods **5**:103, 1936.



Diagrammatic representation of the embryogenesis of absence of the transverse aortic arch and aortic origin of the right pulmonary artery: *A*, normal relationship prior to defective development; *B*, defective development indicated; *C*, defects completed; *D*, defects as found in present care.

CLINICAL OBSERVATIONS

A white male infant weighing 2 kg. was delivered without complications from a 30-year-old secundigravida who said that she had not experienced any illness during the pregnancy. The condition of the newborn was considered good, and it was not until the following day that a poor color and cyanosis were noted. At this time, the lungs seemed to be well aerated, and a loud systolic murmur could be heard over the heart. Despite continuous oxygen therapy, the cyanosis deepened and dyspnea developed, followed later by twitching of the extremities. Death occurred 53 hours after birth.

AUTOPSY

The only significant finding concerned the heart and its great vessels. The heart had a normal configuration except for a slight, predominantly right ventricular enlargement. On section there was a defect, 4 by 7 mm., in the membranous portion of the interventricular septum associated with enlargement of the left ventricular cavity and flattening of the trabeculae carneae. The atria were normal although a small patency of the foramen ovale, 1 by 4 mm., was present in the inferior portion of the interatrial septum. There were no other cardiac abnormalities.

The pulmonary artery was larger than normal, and its lumen continued with undiminished diameter as the ductus arteriosus. The latter terminated, also with unaltered caliber and with no perceptible demarcation, as the descending aorta. The intima of the ductus presented a finely pebbled and wrinkled appearance of slightly darker hue than the smooth, glistening intima of the pulmonary artery. There was no right branch of the pulmonary artery. However, the left pulmonary artery was given off at the usual location.

The aorta was represented by a trunk of average dimension which terminated 14 mm. above the commissural level by dividing into the right innominate and left common carotid arteries. The right pulmonary artery took origin from the right lateral border of the aorta, 3 mm. proximal to the beginning of the innominate artery. It formed an angle of 135 degrees with the aorta and ended in a normal manner in the right lung. Like the left pulmonary artery, it was 3.5 mm. in diameter. There was no connection between the ascending and descending portions of the aorta. The left subclavian artery arose at the junction of the ductus arteriosus and the descending aortic arch.

The other measurements were as follows:

Distance from apex of heart to its base	35 mm.
Diameter of base of heart	32 mm.
Circumference of base of heart	87 mm.
Thickness of left ventricular wall	6 mm.
Thickness of right ventricular wall	4 mm.
Circumference of aorta	17 mm.
Circumference of pulmonary artery	30 mm.

COMMENT

According to Arey,[6] the pulmonary artery develops from a downward growth of vessels from the sixth aortic arches. These vessels, one on each side, meet and fuse with similar vessels growing out from the lungs. Normally, the dorsal portion of the right sixth aortic arch, that is the segment between the aorta and the pulmonary artery, disappears while the dorsal portion of the left sixth arch persists

6. Arey, L. B.: Developmental Anatomy: A Textbook and Laboratory Manual of Embryology, ed. 5, Philadelphia, W. B. Saunders Company, 1946.

as the ductus arteriosus. In the present case there is a persistence of this dorsal segment of the right sixth aortic arch accounting for the communication which exists between the right pulmonary artery and the aorta, and it is to be explained by the abnormal closure or the failure of development of the ventral portion of this arch.

The origin of the transverse arch of the aorta is from the left fourth aortic arch. Its absence in the present case is caused, therefore, by the lack of development or the abnormal obliteration of this embryologic structure. The patency of the interventricular and the interauricular septum is probably influenced by the unusual pressures within the heart occasioned by the absence of the transverse aortic arch. With the nonexistence of the transverse arch, the blood can reach the greater portion of the body only through the ductus arteriosus which, therefore, becomes large and remains patent.

A diagrammatic representation of the genesis of these anomalies is given in the accompanying figure. A similar explanation of this type of maldevelopment of the right pulmonary artery was given by Doering.[4] Ambrus [5] postulated this defect on a premature involution of the right sixth aortic arch and the substitution in the fourth embryonic week of an anomalous artery from the right fifth aortic arch. This explanation will not find ready acceptance because there is some doubt that the fifth aortic arches develop in the human embryo.[6]

SUMMARY

Absence of the transverse arch of the aorta and origin of the right pulmonary artery from the ascending portion of the aorta were observed in a newborn infant who lived 53 hours. These congenital anomalies are explained on the basis of abnormal closure or failure of development of the left fourth aortic arch and of the ventral segment of the right sixth aortic arch, with persistence of the dorsal segment of the latter arch.

Dr. John C. Hughes placed the clinical aspects of this case at our disposal. Miss Julianne Gross prepared the illustrations.

Notes and News

Notice of Medical Meetings.—The following societies will hold annual meetings in the Hotel New Yorker, New York: (*a*) Histochemical Society, April 7 and 8, 1952; secretary, Dr. R. D. Lillie, National Institutes of Health, Bethesda 14, Md. (*b*) American and Canadian Section of the International Association of Medical Museums, April 9, 1952; secretary, Dr. Harold L. Stewart, National Institutes of Health, Bethesda 14, Md. (*c*) Association of Pathologists and Bacteriologists, April 10, 11 and 12, 1952; secretary, Dr. Alan R. Moritz, 2085 Adelbert Road, Cleveland.

American Registry of Pathology of Nutritional Diseases.—This new unit of the American Registry of Pathology has been recently organized at the Armed Forces Institute of Pathology under the sponsorship of the American Institute of Nutrition and the auspices of the Committee on Pathology of the National Research Council. The main purpose of the registry is to provide for the collection and study of documented pathologic material in the field of nutritional diseases. Further information may be obtained from the Registry of Nutritional Pathology, Armed Forces Institute of Pathology, Washington 25, D. C.

Second National Cancer Conference Announced.—Under the sponsorship of the American Cancer Society, the National Cancer Institute, and the American Association for Cancer Research, the Second National Cancer Conference will be held at the Netherlands Plaza Hotel, Cincinnati, on March 3, 4, and 5, 1952. In addition to papers by guest speakers, there will be panel discussions on selected clinical and research aspects of neoplastic disease. The conference is open to all physicians and will provide an excellent opportunity to review the present status of all aspects of cancer.

Books Received

Die Gesunde und Kranke Wirbelsäule in Röntgenbild und Klinik. By Georg Schmorl, Geh. med.-Rat Prof. Dr. med., and Dr. med. vet. h.c. Second edition, by Herbert Junghanns, Prof. Dr. med. habil. Pp. 281, with 399 illustrations. Price 69 German marks. Georg Thieme, Diemershaldenstrasse 47, (14a) Stuttgart O; agents for U. S. A.: Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1951.

Observations on the General Effects of Injury in Man, with Special Reference to Wound Shock. By R. T. Grant and E. B. Reeve. Pp. 313, with 19 illustrations and 51 tables. Price 8 shillings 6 pence net. Medical Research Council Special Report Series, No. 277, His Majesty's Stationery Office, York House, Kingsway, London, W.C. 2, 1951.

Syndromes nouveaux de pathologie adipeuse. By William A. Blanc, chef de travaux, Institut de Pathologie de Genève. Paper bound. Pp. 256, with 84 illustrations. Price 1200 francs. Masson & Cie, 120 Boulevard Saint-Germain, Paris, 1951.

Recent Advances in Bacteriology. Edited by J. H. Dible, M.B., F.R.C.P., professor of pathology, Postgraduate Medical School of London, The University of London. Third edition, by J. D. MacLennan, M.B.E., M.D., research associate, Columbia University Department of Surgery, New York. With the assistance of Mary Barber, M.D., reader in bacteriology, St. Thomas's Hospital Medical School. Pp. 325, with 14 illustrations and 11 tables. Price $5. The Blakiston Company, 1012 Walnut St., Philadelphia 5, 1951.

Topographische Ausdeutung der Bronchien im Röntgenbild. By Priv.-Doz. Dr. Med. Claus Esser, Mainz. Fortschritte auf dem Gebiete der Röntgenstrahlen vereinigt mit Röntgenpraxis, Vol. 66. Pp. 152, with 77 illustrations. Price 33 German marks. Georg Thieme, Diemershaldenstrasse 47, (14a) Stuttgart O; agents for U. S. A.: Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1951.

Curare and Anti-Curare Agents. By K. R. Unna, D. Bovet, W. D. M. Paton, and 28 other authors. Annals of the New York Academy of Sciences, Vol. 54, Art. 3. Pp. 240, with numerous illustrations. Price $4. New York Academy of Sciences, New York, Oct. 30, 1951.

Biological Antagonism—The Theory of Biological Relativity. By Gustav J. Martin, Sc.D., research director, The National Drug Company, Philadelphia. Pp. 516, with 64 illustrations and 44 tables. Price $8.50. The Blakiston Company, 1012 Walnut St., Philadelphia 5, 1951.

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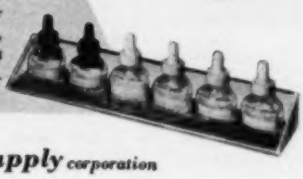

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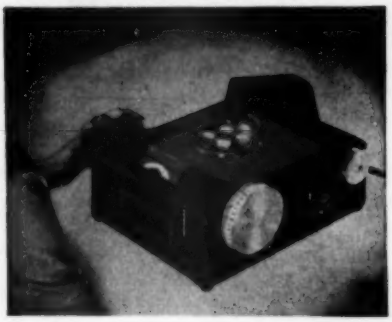

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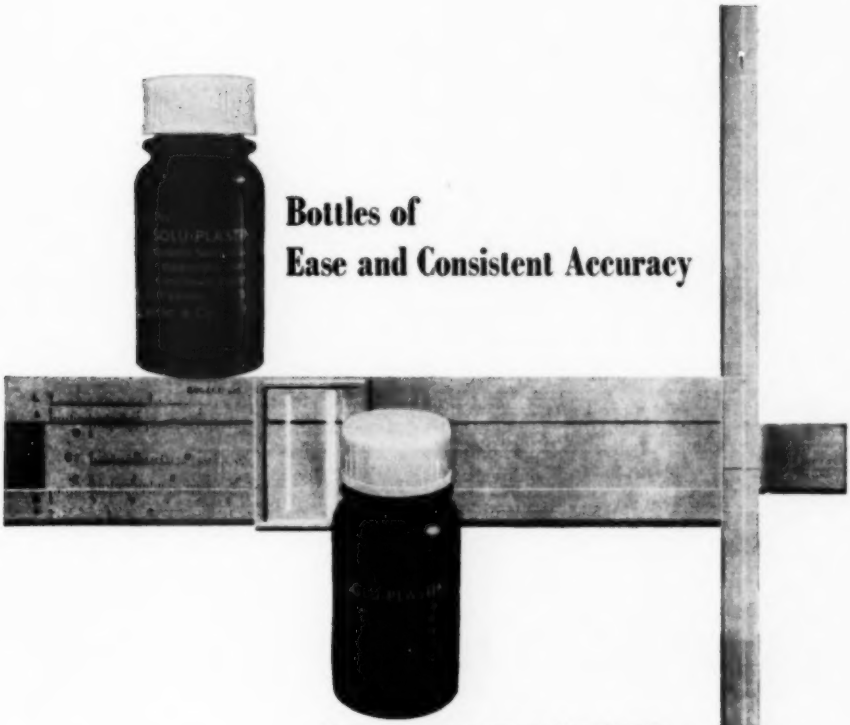

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